STUDIES ON THE CIMETIDINE RESISTANT DUODENAL ULCER

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1982

"A DISCOVERY IS RARELY THE WORK OF ONE MIND. IT IS ONE OBSERVATION ADDED TO ANOTHER THAT MAKES THE SUPERSATURATED SOLUTION FROM WHICH THE CRYSTAL OF TRUTH AT LAST PRECIPITATES?"

Sir Berkely Moynihan 1917

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DECLARATION

The work in this thesis was performed while I was employed as a Research Fellow in Gastroenterology at the Royal Naval Hospital, Haslar, I wrote all the protocols and analysed all the results. Although the initial idea to study the nonresponders was that of Dr. R.H. Hunt, it was left to me to decide what aspects to investigate.

It was my idea to look at pepsin secretion, impromidine stimulated secretion, and the combination of cimetidine with atropine.

I was present during every study reported in this thesis, but was helped with the collection of gastric secretion by Maxine Buck, Angela Paul, and JanMcEwan to whom I am grateful.

I had no part in studying the unselected duodenal ulcer patients described in Experiment 3, who were used for comparison with the non-responders. These patients were all studied under the supervision of Dr. R. H. Hunt who allowed me to use the data.

This work has not yet been published other than in abstract form.

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Date

ABSTRACT - This thesis investigates why some patients with duodenal ulcer do not respond to H_2 blockade and how these patients should be treated.

Part 1 examines the effect of cimetidine 1g/day, cimetidine 2g/day and vagotomy on nocturnal gastric secretion in nonresponders. Cimetidine in either dose had no significant effect on volume of gastric secretion but nocturnal intragastric acidity did show a significant decrease. Vagotomy significantly decreased both volume and acidity of secretion. These findings suggest that nonresponse to cimetidine may be due to increased vagal drive.

Part 2 investigates vagal function further by measuring nocturnal pepsin secretion in patients receiving cimetidine and ranitidine. Both H_2-receptor antagonists increased nocturnal pepsin secretion despite reducing acid. Previous reports suggest cimetidine inhibits pepsin output. However, patients whose acidity is controlled well with cimetidine have a rise in pH which, as pepsin is unstable at high pH values may result in pepsin deactivation . Patients whose acidity is only poorly controlled with cimetidine, therefore, do not denature pepsin, and as H_2 blockade increases vagal drive, intragastric pepsin rises. Duodenal ulcer activity correlates well with pepsin output. Thus, combination of poor acidity control with rise in intragastric pepsin results in nonresponse.

Studies were also performed to investigate the mechanism of increased pepsin secretion. These suggested that histamine may inhibit vagal drive and, therefore, H_2 blockade may increase vagal release. Cimetidine in combination with atropine 4.8mg/day resulted in a significant reduction of volume, acid and pepsin secretion. This latter result suggests that cimetidine should be combined with an anticholinergic agent to inhibit vagal drive and improve control of gastric secretion which theoretically should provide improved clinical response to medical treatment.

CHAPTER I

INTRODUCTION

It has long been recognized that histamine is a potent stimulant of gastric secretion, yet conventional antihistamines are of no benefit in controlling gastric secretion. A leading article in the British Medical Journal in 1948 stated that "it is strange that on gastric secretion alone, there has till now been no suggestion of antagonism between substances (histamines and antihistamines) which are antagonists everywhere else. It is likely that there is one simple explanation of this anomaly which should well repay exploration". It was not until 1972 that Black and colleagues finally provided this explanation by defining the H_2 receptor (Black, Duncan, Durant, Ganellin and Parsons, 1972). Since their report, numerous H_2-receptor antagonists have been developed.

Clinical trials have shown these drugs to be efficacious in treating peptic ulceration without side effects. Few drugs have such widespread use. Indications for treatment have included: oesophagitis (Bennet, McCormick, Oliver, Celestin, 1978; Heading, Blackwell, Cameron, 1981), gastric erosions (Speranza, Basso, Bagorcine, Bianchi, Materia, Firoani 1979(, emergency anaesthesia (Moore, Howe, Dundee, Johnston, McCaughey, 1981), renal transplantation (Vanrenterghem, Roels, Michielsen, 1980), pancreatic insufficiency, and ileal resection (Northfield, Zentler-Munro, Fitzpatirck, Fine, 1981), as well as gastric and duodenal ulceration with their associated complications.

Despite enormous success, cimetidine does not heal all duodenal ulcers. After a six week course of therapy, healing rates are reported around 75% with some 25% remaining unhealed (Burland, Hunt, Mills, and Milton-Thompson, 1979). It is, at present, not known how these cimetidine resistant ulcers should be treated and why they do not respond to H_2 blockade. This thesis attempts to answer these two questions.

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1.1 The problem of peptic ulceration. It has been estimated that in the Western World, 10-15% of men and 4-15% of women are afflicted with at least one attack of peptic ulcer during their lifetime (Venables 1979). Studies from the United States, the Netherlands, Italy, and Sweden have estimated that the total cost of peptic ulcer disease is 1% of the cost of all diseases (Bodemar, Gottherd, Ström, Walen, Jönsson, Bjurulf 1979). Approximately 1.5% of all days off work in the U.S.A. in 1975 were due to peptic ulcer, costing an estimated 1330 million dollars which was equivalent to 18.6 million working days (Bodemar, Gottherd, Ström, Walen, Jönsson, Bjurulf 1979). In England and Wales, approximately 20 million working days are lost each year because of upper gastro-intestinal symptoms (Langman 1978).

Although the introduction of cimetidine brought a decrease in the number of working days lost from duodenal ulcer disease (Bardhan 1981a; Bodemar and Walen 1978), this decrease was only about 10% between 1974-75 and 1978-79 (Bardhan 1981a).

The cost of surgery for duodenal ulcer is difficult to estimate. Inpatient stay after vagotomy is estimated at 15.1 days (Pounder 1981) and inpatient treatment in the National Health Service in March 1981 was £75.00 per day. On these figures, the cost per operation is £1133 which does not include loss of earnings or the costs of recurrent ulcer after surgery.

Culyer and Maynard (1980) put the loss of earnings after vagotomy at £1660 and suggested that the cost of surgery to the community was in the region of £16000 per patient.

Although cimetidine has reduced the number of elective operations for duodenal ulcer (Coggan, Lambert, Langman 1981; Venables 1981; Hunt 1981a; Fineberg and Pearlman 1981), there were still some 660 operations per year performed for duodenal ulcer in the Northern

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Region of the United Kingdom between 1977 and 1979.

1.2 The aetiology of duodenal ulcer. Present thoughts on the aetiology of peptic ulceration suggest an imbalance between mucosal barrier versus acid and pepsin secretion. The logical approach to treatment has, therefore, been chanelled in one of these directions.

1.3 The mucosal barrier. Claude Bernard (1856) likened the stomach to a perocelain pot, so introducing the concept of a mucosal barrier. This concept is thought to be a dynamic equilibrium depending on gastric mucosal blood flow (Moody, McGreevy, Zalewsky, Cheug, Simmons 1978; Guth, Bauman, Grossman, Aures, Elashoff 1978), cellular regeneration, secretion of mucus, epidermal growth factor, prostaglandins (Grossman 1980), bicarbonate (Garner and Flemstrom 1978) and hydrogen ions together with a dynamic gradient of acid concentration across the mucous lining of the stomach (Rees and Turnberg 1981; Bahari, Rees, and Turnberg 1981).

Caved S (deglycyrrhizinated liquorice) (Morgan, McAdam, Pacsoo, Darnborough 1982; Tewari, and Trembalowics 1968), Denol (tripotassium dicitrato bismuthate) (Martin, Hollander, May, Ravenscroft, Tweedle, Miller 1981), carbenoxolone (Morgan, McAdam, Pacsoo, Walker, Simmons 1978) and sucralfate (Marks, Wright, Denyer, Garish, Luck 1980; Martin, Farley, Gangon, Bensemana 1982) are all thought to act on the mucosal barrier and have been shown to be of benefit in healing gastric ulcer. Some reports also suggest these compounds are useful in duodenal ulcer (Morgan, McAdam, Pacsoo, Darnborough 1982; Martin, Hollander, May, Ravenscroft, Tweedle, Miller 1981; Reed and Davies 1978; Hollander 1981).

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1.4 Pepsin. In 1752, Réaumir showed that meat was digested without putrefaction by the regurgitated contents of his pet buzzard. His findings were confirmed by Spallanzani (1783) using human gastric juice. The proteolytic action of gastric juice was named "pepsin" by Schwann in 1836.

The amount of pepsin in gastric juice may be measured using its proteolytic activity to digest a known amount of haemoglobin substrate, measuring the colour change spectrophotometrically, and comparing the results with a known amount of crystalline hog pepsin treated in the same way (Anson and Mirsky 1932). This technique may be improved by using modified haemoglobin substrate (Berstad 1970) or radioactive iodinated albumin (Klotz and Duvall 1957) but the basic method remains the same. Unfortunately, these analyses are time consuming because they require incubation of gastric juice with substrate followed by separation of substrate and products. They also suffer from not being reproducible between centres because of the variable purity of commercially available hog pepsin.

It is generally thought that in the basal state, pepsin output parallels acid output (Janowitz and Hollander 1952; Hirschowitz and London 1955; Woodward, Schapiro, Armstorng 1956; VanGoidsenhoven, Wilkoff, Kirsner 1958). However, pepsin becomes denatured at high pH values (Goulding, Borsook and Wasteneys 1927; Piper and Fenton 1964; Berstad 1982) and, therefore, low acid outputs with associated high pH values will result in an apparently low pepsin output.

Vagal stimulation results in greater increase in pepsin secretion than acid secretion and although pentagastrin is a potent stimulant of acid, it is not as potent at stimulating pepsin release (Venables, Wheldon, Johnston 1975; Venables and Johnston 1969; Wilson, Dymock, Cowley 1974; Berstad, Peterson, Roland, Liavig 1973). Thus different

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mechanisms exist for controlling acid and pepsin secretion.

The greater secretion of pepsin after vagal stimulation has been used clinically by Venables, Wheldon and Johnson (1975) and Gulvag and Berstad (1982) who found that output of pepsin after a vagal stimulus was a better prediction of the completeness of vagotomy than was acid output.

According to Pollard and Augur (1968), Quincke first used the term "peptic" in 1882 to describe a gastric ulcer, yet in the present day, this term is used for any mucosal defect in the upper gastrointestinal tract brought about by the action of acid and pepsin. The term obviously implies that pepsin has a major role in the aetiology of this disease. During perfusion experiments on cat stomach, duodenum and jejunum, Schiffrin and Warren (1942) demonstrated that acid alone did not produce ulceration unless combined with pepsin. They suggested that acid ulcer was a misnomer and that more attention should be directed to the inactivation of pepsin in the treatment of duodenal ulcer.

Although Hunt (1950a; 1950b) found no relative hypersecretion of pepsin in patients with duodenal ulcer, most other workers have noted increased intragastric pepsin secretion when compared with normal individuals (Venables 1969; Taylor 1970) and pepsin output has been related to disease activity (Vanzant, Osterberg, Alvarez, Rivers 1933; Taylor 1970; Venables 1969; Venables 1971; Elder 1975; Achord 1978). Bonfils, Lewin, Vatier, Dubrasquet and Bader (1968) found a small number of patients with excess pepsin secretion whom they classified as having increased vagal drive; Pelican, Horcicka and Komenda (1969) also found a group of patients with low basal acid and high basal pepsin output who they suggested had a high vagal tone.

Despite these reports, compounds which neutralize pepsin have not received as much attention as those which neutralize acid. In the

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lay literature, novelist P.G. Wodehouse (1921) had one of his characters asking for "pepsin" to cure his indigestion. Even in the medical literature, pepsin inactivation does not receive much attention. In a recently published 552 page book entitled "Advances in Ulcer Disease. Proceedings of a symposium on the pathogenesis and therapy of ulcer disease" (Holtermüller and Malagdelada 1980) pepsin received only one paragraph which described how it may be inactivated by antacids.

Babkin and Komorov (1932) were the first to search for an antipepsin agent. Others have tried using:pepstatin (Umezawa, Aoyagi, Morishima, Matsuzaki, Hamada, Takeuchi 1970; Christiansen, Svendsen, Guldager, Christensen 1975), amylopectin (Sun and Ryan 1970; Cayer and Ruffin 1967), carrageenin (Anderson and Watt 1959), aluminium sucrose sulphate (Yagamato, Ishimori, Sato et al, 1973), chondroitin sulphate (Cook and Drill 1967) and hydrotalcite (Playle, Gunning, Llewellyn 1974). Amylopectin has been shown to improve healing of gastric ulcer but all the other agents are of no proven benefit - even when combined with an anticholinergic agent to delay gastric emptying (Cocking 1972). One possible explanation for this lack of effect of antipeptic agents is that duodenal ulcer patients have high basal pepsin outputs and, therefore, large quantities of inactivator should be necessary to promote healing.

Anticholinergic agents inhibit secretion of both acid and pepsin but if they are to be of clinical benefit, they need to be given in large doses which cause distressing side effects (Ivey 1975).

1.5 Acid. In 1823, William Prout reported to the Royal Society that the vomitus of three patients with dyspepsia contained free muriatic (hydrochloric) acid "in great abundance". Prout's observations were confirmed by William Beaumont (1833) during studies on his famous patient, Alexis St. Martin, but it was not until 1910 that Schwartz

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introduced the dictum "no acid - no ulcer". Since that time, decreased acid secretion has formed the mainstay of treatment for duodenal ulcer for the following reasons:

1) Despite a few reports (Janowitz and Hollander 1951; Greenspan, Levy and Nechels 1951; Watkinson and James 1951; Schiff, Pugh and Watkins 1962; Isenberg, Spector, Hootkin and Pitcher 1971; Korn and Faroozan 1974; Wald and Burbige 1975) which have been challenged (Baron 1963; Baron 1975), it is generally believed that duodenal ulceration in the presence of anacidity is extremely rare.

2) A duodenal ulcer is highly likely in the presence of a peak acid output of greater than 50 mmol/hr (Baron 1973).

3) Duodenal ulcer is rare in patients with peak acid outputs of less than 15 mmol/hr (Baron 1973).

4) A duodenal ulcer is usually present in the Zollinger-Ellison syndrome (Zollinger and Ellison 1955) with its associated hypersecretion of acid.

5) Measures which decrease acid output by medical or surgical means usually result in ulcer healing.

Prior to the introduction of the histamine H_2-receptor antagonists, no really effective medical therapy was known for the treatment of duodenal ulcer. Antacids decrease intragastric acidity over a twenty-four hour period (Keenan, Hunt, Vincent, Wright and Milton-Thompson 1978) and have been shown to heal duodenal ulcers when given in large doses (Peterson, Sturdevant, Franki et al 1977; Ippoliti, Sturdevant, Isenberg et al 1978). However, high doses of antacids are associated with significant side effects (Spencer and Lender 1979).

Several workers have tried to identify gastrin inhibitors Gregory and Ivy 1941; Uvnas 1942) and others have tried dietary manipulation (Lennard-Jones 1965) in an attempt to decrease intragastric acidity. None of these has any effect on the healing of duodenal ulcer.

1.6 The importance of histamine. Histamine was first synthetised in 1907 (Windus and Vogt), but it was not until 1920 (Popielski) that it was shown by work in dogs to be a potent stimulant of gastric secretion. Carnot, Korskowski and Libert (1922) demonstrated a similar effect in man.

Barger and Dale (1911) had identified histamine in extracts of intestinal mucosa but it was left to Best, Dale, Dudley and Thorpe (1927) to establish beyond doubt that histamine occurred naturally in the body and was not a contaminant of tissue extracts.

Vagal stimulation was shown to result in histamine release in the gastric lumen suggesting that histamine may have been a final common pathway (Babkin, 1938). Emmelin and Kahlson (1944) concluded that "during the cephalic and gastric phases, parietal secretion is excited by a two state humoral mechanism, the first stage involving the liberation of gastrin, and histamine representing the second final link".

Code (1956) proposed "no other chemostimulator is interpaired between histamine and the parietal cell. Histamine is the final common local chemo-stimulator of the parietal cells of the gastric mucosa". This theory has been challenged (Grossman 1967; Johnson 1971) and more recently, Soll (1978) using isolated parietal cells has suggested that histamine employs a permissive role in gastric secretion.

In 1937, Bovett and Straub demonstrated 2-isopropyl-5-methyl phenoxyethyldiethylamine antagonised some of the actions of histamine yet antagonism of other actions of histamine such as gastric secretion were not affected. Other attempts to antagonise gastric secretion with conventional antihistamines all resulted in failure (Moersh, Rivers, and Marlock 1946; Emmelin and Frost 1947; Ashford, Heller and Smart 1949; Doscherholmer 1949).

Kay (1953) utilised the lack of effect of conventional antihistamines on gastric secretion by using these compounds in combination

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with histamine to develop his augmented histamine test. Ash and Schild (1966) suggested calling the effects of histamine antagonised by anti-histamines H_1 effects, but it was not until 1972 that the H_2 receptor was defined.

1.7 The introduction of Cimetidine. In 1972, Black and his colleagues demonstrated that the first H_2-receptor antagonist, buriamamide, inhibited histamine and pentagastrin stimulated gastric acid secretion by 57%. The absorption of the drug was found to be unreliable in experimental animals and no further evaluation of this compound was performed in man. Slight alteration in the chemical structure of burimamide resulted in a compound with improved solubility and ionisation, hence providing better absorption. The resulting compound, metiamide, was found to be more potent than burimamide in decreasing stimulated acid secretion and reached the stage of clinical trials to assess healing in duodenal ulceration.

Unfortunately, although it was shown to be efficacious in healing duodenal ulcer, 7 cases of bone marrow depression were reported, one of whom died (Burland, Sharpe, Colin-Jones, Turnbull and Bowskill, 1975). Metiamide was, therefore, withdrawn from all further use in man.

Cimetidine was the third H_2-receptor antagonist to be synthetised and was found to be without side effects or adverse reactions in experimental animals. It was shown to effectively inhibit all forms of stimulated gastric acid secretion in man (Burland and Mills, 1979; Longstreth, Go and Malagelada 1976; Carter, Forrest, Logan, Ansell, Lidgard, Heading and Shearman, 1976; Pounder, Williams, Russell, Milton-Thompson and Misiewicz 1976; Schoon and Olbe 1977) and numerous clinical trials have confirmed its efficacy at both relieving symptoms and healing duodenal ulceration (Bodemar and Walan 1976; Gray,

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McKenzie, Smith, Crean, and Gillespie 1977; Bardhan 1979).

Cimetidine dramatically altered the management of peptic ulcer disease. For the first time, it was possible to effectively control acid secretion over a prolonged period of time without resorting to surgery. Cimetidine was introduced on the open market in the United Kingdom in 1976 (Duncan and Parsons 1980), and in the United States in 1977. Since its introduction, over 15 million patients have been treated worldwide, and in the United States an estimated 1 in 50 of the population have been given the drug (McGuigan 1981). Several other H_2-receptor antagonists are at present under investigation and one of these, ranitidine, has recently been introduced on open prescription in this country.

Cimetidine was shown to be a relatively safe drug. In short term clinical trials of 2,182 peptic ulcer patients, treatment with cimetidine resulted in withdrawal of 24 (1.5%) patients because of untoward side effects compared to 10 (1.2%) of 844 patients treated with placebo (Burland, 1978).

During the 20 years before the introduction of cimetidine, it had been noted that there had been a steady decline in both hospital admissions and mortality from peptic ulcer. This observation had been made in this country (Coggan, Lambert and Langman 1981; Langman 1982) and abroad (Fineberg and Pearlman 1981). This decline has been dramatically accelerated by cimetidine. Venables (1980) reported that the number of elective operations performed in his unit fell from 54 per year before 1976 to 29 per year in 1977 - an overall reduction of 47%. Other authors have reported a similar trend (Wyllie, Clark, Alexander-Williams, Bell, Kennedy, Kirk and McKay 1981; Coggan, Lambert and Langman 1981; Fineberg and Pearlman 1981). More recently however, it has been recognised that not all patients benefit from these drugs

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and surgery is still required in some cases.

1.8 Medical treatment after cimetidine. Since the introduction of cimetidine, there have been many clinical trials assessing new methods of treatment. Most of these trials use cimetidine as a standard to assess healing at it is now unethical to compare any new treatment with placebo (Marks, Wright, Denyer, Garish and Luck 1980; Morgan, McAdam, Pacsoo, Walker and Simmons 1978; Martin, Hollander, May, Ravenscroft, Tweedle and Miller 1981).

As cimetidine provides healing rates around 75%, extremely large numbers are required to show a statistically significant benefit using other treatments. For example, if a new therapy was found to have a healing rate as high as 20% above that of cimetidine in a trial of 100 patients, there would only be a 50% chance of this being significant at the 5% level. Thus, it is extremely difficult to show any treatment is superior to cimetidine.

As more experience is gained with cimetidine, more side effects are being noted. Mental confusion may occur in the elderly or very ill in whom cimetidine may cross the blood brain barrier (Roley-Jones, Flind and Backhouse 1980). Cimetidine has mild antiandrogenic effects in animals in much higher doses than that which are used clinically (Burland 1978). It causes an increase in serum prolactin when given as an intravenous bolus in man and has been shown to elevate serum LH and testosterone (Knigge, Wollesen, Dejgarrd, Thuesen and Christiansen 1981; Edwards and Rilley 1981). It also decreases the response of aldosterone to angiotensin, inhibits vasopressin release and causes an exaggerated response of TSH to a TRH stimulation test. Reported side effects have included gynaecomastia, impotence and loss of libido (Edwards and Rilley 1981). It has also been shown that cimetidine

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interferes with hepatic metabolism of other drugs such as warfarin, diazepam, phenytoin and antipyrine (Henry, MacDonald, Kitchingman, Bell and Langman 1980; Serlin 1981; Babb 1981). More recently there have been reports of arthropathy (Committee of Safety of Medicines 1981a) and renal failure (Payne, Ackrill and Ralston 1982) associated with cimetidine therapy. Early experience with ranitidine suggests that the latest H_2-receptor antagonist is without most of these problems, although two reports (Knigge, Wollensen, Dejgarrd, Thuesen and Christiansen 1981; Lombardo 1982) have shown an increase in serum prolactin with ranitidine.

One of the most serious risks of cimetidine is the ability to suppress the symptoms or even heal an early intramucosal gastric carcinoma or lymphoma and thus delay diagnosis. Even an experienced endoscopist can miss small lesions on the lesser curvature and it seems likely that a missed carcinoma was present before cimetidine treatment in all of the twenty-one patients with gastric carcinoma in association with cimetidine treatment reported to the Committee of Safety of Medicines up to January 1981 (Committee of Safety of Medicines 1981b).

A further association between cimetidine and gastric cancer has been suggested by two hypothetical mechanisms. The first suggests that by raising intragastric pH, colonisation of the stomach by nitrate reducing bacteria might increase intragastric nitrite and subsequently nitrosamines and nitrosamides which theoretically might be associated with an increased risk of gastric carcinoma (Ruddell, Axon, Findlay and Bartholomew 1980). Hunt, Vincent, Kelly, Perry and Milton-Thompson (1980), however, have shown that vagotomy is even more effective at raising pH than cimetidine and Stalsberg and Taksdal (1971) have shown a six-fold increase in the risk of gastric carcinoma following gastric surgery. Moreover, recent work (Milton-Thompson

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Lightfood, Ahmet, Hunt, Barnard, Bavin, Brimblecombe, Darkin, Moore and Viney 1982; Muscroft, Youngs, Burdon and Kieghley 1981) casts coubts on this theoretical risk by showing that in normal subjects on a normal diet, cimetidine 1g/day does not alter pH sufficiently to produce bacterial colonisation, nor are there any consistent changes in nitrate reducing bacteria, nitrite or nitrosamine levels.

A more worrying hypothesis is that intragastric nitrite may combine with cimetidine, resulting in nitrosocimetidine which is of similar chemical structure to MNNG (N-methyl-N-nitroso-N-nitrosoguanidine), a known potent gastric carcinogen in animals (Elder, Ganguli and Gillespie 1979). Nitrosocimetidine, however, has never been isolated from the stomach in man. Many other drugs such as chlorpromazine, chlordiezepoxide, tetracycline and oxytetracycline also undergo nitrosation producing theoretically carcinogenic metabolites yet malignancy has not been reported in association with any of these drugs.

Despite these theoretical risks, cimetidine is probably the drug of choice for duodenal ulcer at the present time.

1.9 The surgical treatment of duodenal ulcer. The surgery of peptic ulcer has changed considerably over the last century. Gastrectomy became popular after Péan (1879) demonstrated this procedure was technically possible. Unacceptably high morbidity and mortality, even in experienced hands, resulted in the introduction of other alternatives (Visik 1948).

Wofler, Bilroth's assistant, (1881) performed the first gastroenterostomy for malignant disease and this soon replaced gastrectomy in the treatment of duodenal ulcer. The first report of stomal ulceration following gastroenterostomy appeared in 1899 (Braun) and soon afterwards Mayo (1902) reported a 25% recurrence rate in a

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personal series of 102 gastroenterostomies.

Pavlov (1910) noted vagotomy decreased acid secretion in the dog, and Laterjét (1921) suggested using vagotomy for treating duodenal ulcer. Section of the vagus nerves in man was shown to decrease intragastric acidity in 1929 (Hartzell), but it was left to Dragstedt and Owens (1943) to popularise the operation.

Laterjét had recommended a gastroenterostomy with vagotomy and although at first Dragstedt and Owens (1943) did not recommend drainage, later reports (Dragstedt 1945) suggested this could avoid problems with stasis.

Colp (1950) was dissatisfied with high recurrence rates after vagotomy and combined this procedure with antrectomy. Others found diarrhoea and dumping unsatisfactory complications after vagotomy and pylorplasty and introduced selective vagotomy (Griffiths and Harkins (1957) and proximal gastric vagotomy (Amdrup and Jensen 1970; Amdrup, Johnson and Goligher 1970; Johnston and Wilkinson 1970). Although diarrhoea and dumping are less after proximal gastric vagotomy (Gillespie 1982), they are still recognised complications of this form of surgery (Humphrey, Johnston, Walker, Pulvertaft and Goligher 1972) and some authors report a 15-20% recurrent ulcer rate (Blackett and Johnston 1981; Venables 1980; Gillespie 1982).

As the treatment of choice, surgery carries unacceptable morbidity and mortality and should, therefore, only be performed when indicated. An operation is a relatively high price to pay for what is essentially a benign disease characterised by only short exacerbations and prolonged remissions. Indications for surgery included failed medical treatment or complications such as bleeding, perforation and stenosis. Contra-indications include poor physical health and mild or infrequent attacks.

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Cimetidine has not altered these indications although may have decreased their incidence.

In 1950, Colp wrote "in our experience less than 15% of patients suffering from duodenal ulcer fail to respond either permanently or temporarily to effective medical treatment". Although this figure was not supported by any data, it is interesting to note that it is less than the present estimates of those patients who do not respond to H_2 blockade.

1.10. The cimetidine nonresponder. It is becoming increasingly recognised that cimetidine will only heal between 57 and 87% of duodenal ulcers after a six week course of therapy (Burland, Hunt, Mills, Milton-Thompson 1977; Bardhan 1981). Although in most cases, continued treatment ultimately results in healing, the pattern of response is predictable in that some 7 in every 100 patients with duodenal ulcer have more than three attacks per year (Bardhan 1980).

Several questions need to be answered about patients who fail to respond to cimetidine. Firstly, why do they not respond; secondly, is any other medical therapy effective and finally, if surgery is indicated, do these patients have a good result from vagotomy or should more radical surgery be performed?

One possible explanation for nonresponse is poor compliance. Boyd, Wilson and Wormsley (1982) have monitored compliance by counting tablets and measuring drug metabolites in early morning urine samples. They concluded that compliance did not differ between patients whose ulcer remained healed and those who relapsed. This is not really surprising because patients with active ulcer disease experience pain which gives them an incentive to take their tablets.

Once symptoms disappear, compliance may not be important because a recent study (Lance and Gazzard 1982) has shown that the number of

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ulcers that can be shown to have endoscopically healed three months after presentation, is independent of the length of treatment, as long as the patients take their tablets until symptoms disappear.

Boyd, Wilson and Wormsley (1982) have also shown that patients who relapse on maintenance therapy are no different from those who do not as regards age, sex, duration of history, smoking habits and alcohol consumption. These findings have been confirmed by Bardhan (1981b) who called the cimetidine resistant ulcer "refractory ulcer". Bardhan has also shown no significant differences in endoscopic features, acid and pepsin outputs and serum gastrin levels when compared to non-refractory ulcer patients (Bardhan 1981c).

Peden, Boyd and Wormsley (1981) found women less likely to heal their ulcer but Sonnenberg and colleagues (1981) found an increased incidence of healing in women. They also found moderate alcohol intake, abstinence from smoking and young age were good prognostic indicators whereas concomitant disease, number and total area of peptic lesions, family history and duration of history had no influence on whether the ulcer responded to treatment.

Dragstedt (1945) suggested that the most important aetiological factor in the pathogenesis of duodenal ulcer was increased vagal drive manifested by nocturnal hypersecretion. More recently, Hunt (1981) has noted that although during the daytime, individual responses to cimetidine are similar, overnight there are two patterns of response; one group of patients show little or no decrease in hydrogen ion acitivity when receiving cimetidine, whereas a second group become relatively anacidic. When looked at retrospectively, the former group of patients were noted to have a poor response to treatment.

There have been two reports of increased basal acid output in cimetidine nonresponders (Hetzel, Hansky, Shearman, Korman, Hecher,

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Taggart, Jackson and Gabb, 1978; Cargill, Peden, Saunders and Wormsley 1978) but Longstreth and Malagdelada (1976) found spontaneous rate of acid secretion was of no value in predicting response to the drug. Binder and colleagues (1978) recorded increased peak acid output after betazole in nonresponders and Hetzel, Hansky, Shearman, Korman, Hecher, Taggart, Jackson and Gabb (1978) noted increased peak acid output after pentagastrin although did not find this significant. Others (Hunt, 1981; Boyd, Wilson and Wormsley 1981; Bardhan 1981b) have not found increased basal or peak acid outputs in nonresponders.

Kirkpatrick and Hirschowitz (1980) reported 12 hypersecreting duodenal ulcer patients whose basal acid output was resistant to cimetidine therapy, but decreased by 90% with atropine, inferring cholinergic drive. A group of duodenal ulcer patients with a high basal acid output which did not greatly increase with sham feeding made Feldman, Richardson and Fordtran (1980) conclude that some patients have increased vagal drive although did not relate this with nonresponse to cimetidine.

Venables (1980) using a combined pentagastrin/insulin test has shown that after insulin stimulation, the usual relationship between acid and pepsin secretion is lost in those who heal. This led him to suppose that patients who fail to heal are more responsive to vagal stimulation than those who do heal. This suggestion is also supported by his finding that in ten patients who failed to respond, after randomly receiving either cimetidine and an anticholinergic agent or cimetidine alone, all on the combined therapy healed their ulcer compared to three out of five taking cimetidine alone. Thjodleifsson and Wormsley (1975) have also suggested that when nocturnal acidity is not controlled by H_2-receptor blockade, the degree of gastric inhibition can be increased by atropine, and this observation has

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been confirmed by others (Thompson, Albinus, Blair, Reed, Venables 1975; Barbezat and Banks 1976). Combination of cimetidine with a new locally acting antimuscarinic agent, pirenzepine, has resulted in better acid inhibition than cimetidine alone (Londong, Londong, Weber and VonWerder 1980). The combination has also been shown to improve healing rates of duodenal ulcer compared to either drug used alone (Roberto, Nicola and Sergio 1982).

Increased vagal drive when receiving cimetidine is suggested by the findings of Maybury and Carr-Locke (1980) in that a high relapse rate may be predicted if an insulin test produces the same acid response when receiving cimetidine as when receiving no drug at all.

Vagal stimulation in patients with active duodenal ulcer produces a greater increase in pepsin output than acid output (Roland, Berstad, and Liavag 1974; Clarke, Allan, and Alexander-Williams, 1972; Rosato and McFadyen 1971), and measuring basal pepsin output should be a better indicator of increased vagal drive. Japanese workers (Kishi, Seki, Kilamura and Mori 1978) have found an increased intragastric basal pepsin output and Pikkarainen, Vuoristo and Torpila (1981) found increased serum pepsinogens in patients with ulcers which fail to heal, although Wormsley (1981) and Bardhan (1982) have found no increase in pepsin output in cimetidine nonresponders.

The hypothesis that increased vagal drive results in nonresponse to H_2 blockade is supported by the results of vagotomy. Hypersecreting duodenal ulcer patients described by Kirkpatrick and Hirschowitz (1980) had very good results from vagotomy, as did three patients who met the criteria of nonresponse to cimetidine reported by Hunt et al (Hunt, Vincent, Kelly, Perry and Milton-Thompson 1980). Venables (1980) has reported a 16.6% recurrence rate in nonresponders after proximal gastric vagotomy (PGV) compared to a 5% recurrence rate with truncal

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vagotomy and pylorplasty before the introduction of cimetidine. This high recurrence rate, however, is similar to a 16% recurrence rate with proximal gastric vagotomy in cimetidine failures reported by Blackett, and Johnson (1981):this compared with 14% before cimetidine using the same operation. These high recurrence rates in nonresponders may be due to more accurate diagnosis with the widespread use of endoscopy to document recurrence rather than poor results with highly selective vagotomy.

Before deciding how to evaluate cimetidine nonresponders, it is necessary to discuss the functions of the stomach and the different investigative options.

1.11 The functions of the stomach. These can be broadly divided into motility and secretion. Motility is mainly assessed by measuring the rate of gastric emptying. Several methods are employed using either the dye dilution technique (George 1968) or more commonly radioactive test meals (Griffith, Owen, Kirkman and Shields 1966). Both these methods are fraught with difficulties. The dye dilution technique only measures emptying of liquids and involves the passage of a naso-gastric tube which is not physiological. Rate of emptying depends on not only the position of the patient (Hancock, Bowen-Jones, Dixon, Testat, Dymock and Cowley 1974) but also on the type of marker used; different rates are reported between liquids and solids (Heading, Tothill, McLoughlin and Shearman 1976) and between water soluble and fat soluble markers (Cortot, Phillips and Malagelada 1981). Although Kirkpatrick and Hirschowitz have noted a higher residual volume in nonresponders (Kirkpatrick and Hirschowitz 1980) which they thought might be due to delay in gastric emptying, this thesis has not investigated gastric emptying because of the difficulties with interpretation.

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Leube (1868) was the first to suggest the possibility of studying gastric physiology by aspiration of the stomach contents. Although this method has the disadvantages of being unphysiological and unpleasant for the subject, it is still the best method of obtaining information about gastric secretion.

The stomach secretes acid, pepsin, water, mucus and bicarbonate, all of which have been measured: in a basal state either in the fasted patient (Galambos 1926; Levin, Kirsner and Palmer 1951), overnight (Winkelstein 1935;) or over a twenty-four hour period (Voegtlin 1947; Pounder, Williams, Milton-Thompson and Misiewicz 1976) in a stimulated state using either histaminic (Kay 1953), gastriergic (Wormsley, Mahoney and Ng 1966) or cholinergic stimuli (Wilson, Dymock and Cowley 1974) or a combination of these using food (Von Leube 1871; Fordtran and Walsh 1973); or in an inhibited state employing histamine H_2-receptor antagonists or anti-cholinergics.

Acidity is measured by recording pH using a glass electrode (Moore and Scarlata 1965) and total free acid is measured after titrating a sample of gastric juice to pH7 with sodium hydroxide using an autoburette (Radiometer, Copenhagen) and dividing the number of moles of alkali added by the volume of juice sample. If this figure is then multiplied by the total volume of juice over a given time, total acid output is calculated.

Pepsin is usually measured by the Anson and Mirsky method (1932) which utilizes the digestive properties of pepsin. A known amount of haemoglobin is incubated with gastric juice and after digestion over a period of time, any colour change is measured colorimetrically. When this reading is compared to a known standard amount of crystalline pepsin, a value can be obtained. Methods have evolved to improve the substrate using modified haemoglobin (Berstad 1970) or radioactive

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iodinated albumin (Klotz and Duvall 1957), but all methods suffer from the disadvantage of being time consuming and not always reproducible because of the variable purity of commercially available pepsin.

Bicarbonate may be measured by utilizing various markers with gastric and duodenal tubes (Rees and Turnberg 1981). Numerous calculations are made to allow for pyloric loss and reflux but these obviously decrease the accuracy of the technique. Two nasogastric tubes are also uncomfortable for patients. Similar sophisticated methods are used to measure gastric mucus (Glass 1967; Horowitz 1967) and techniques have evolved to calculate mucoprotective index but these also involve complex calculations (Guslandi, Testori, Fesce, Ballarin and Tittobello 1980).

The main thrust of research into gastric secretion has been directed at acid secretion although even this is not without difficulties. Saliva dilutes gastric juice, secretions are lost via the pylorus and bile refluxes into the stomach so neutralising acid.

Various techniques exist for positioning nasogastric tubes (Hassan and Hobsley 1970) and also for correcting for reflux (Gardham, Hassan and Hobsley 1968) and for pyloric loss using either I^{131} (Johnston 1958) or phenol red (Hobsley and Silen 1969; Hassan, Gardham and Hobsley 1969; Venables 1972). However, these techniques only improve collections by 5% (Hobsley and Silen 1969), and it has been reported that a 98% recovery can be expected using a combination of continuous suction by a mechanical pump interrupted by manual aspiration (Johnston and McGraw 1958). One report (Cook and French 1968) also suggests that phenol red is absorbed from an acid stomach and previous personal experience has found the method to be messy and not always reliable. The main problem of using phenol red is that the standard nasogastric tube has to be modified by the addition of an extra lumen which should be brought to the outside 15 cm from the tip. This often produces

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damage to the tube, so producing an imperfect vacuum for aspirating gastric juice and also sometimes giving the investigator difficulty in passing the tube.

Collection techniques are more accurate if large volumes of secretion are collected (Hassan, Gardham and Hobsley 1969), and as nonresponders have been reported to have large volumes of secretion (Hetzel, Hansky, Shearman, Korman, Hecker, Taggart, Jackson, Gabb 1978; Cargill, Peden, Saunders and Wormsley 1978), studies in this thesis have not utilized a marker.

1.12 Conclusion. The previous review of the literature suggests that there may be several reasons for nonresponse to cimetidine but increased vagal drive appears to be of particular importance. Dragstedt (1945,) has suggested that increased vagal tone is manifest by nocturnal hypersecretion and it was, therefore, decided to first investigate secretion during the overnight period. The night time was also felt to be of particular importance because Hunt (1982) had observed a distinct difference between responders and nonresponders during the night but not during the day. The initial studies in this thesis, therefore, looked at nocturnal gastric secretion in nonresponders compared to a group of duodenal ulcer patients who had been studied previously at the Royal Naval Hospital, but who were not selected as being a responder or nonresponder. The first studies also investigated how nocturnal secretion was modified by an increased dose of cimetidine, by combination of cimetidine with atropine and by surgery.

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PART I

ACID

CHAPTER 2

METHODS

2.1 Patients. Any criteria chosen to define a nonresponders must be done arbitarily. Continued treatment with cimetidine improves the number of ulcers which heal (Bardhan 1980) and, therefore a specific period of treatment must be defined.

It is also known that relapse on maintenance therapy is higher than on full dose treatment (Pounder 1981; Bardhan 1981) and therefore a dose of treatment must also be defined. Cimetidine may relieve symptoms without healing the ulcer (Bardhan 1981b) and some patients who stop treatment, relapse early because their ulcer was not healed. There will often be a delay in diagnosing relapse in these patients because they may either delay in reporting symptoms or endoscopy may be delayed because of hospital waiting lists. The criteria chosen for a cimetidine nonresponder in this thesis included:

1) Failure to heal after cimetidine 1g/day for 6 weeks
2) Relapse on maintenance therapy of 400mg nocte
3) Relapse within a month of stopping cimetidine 1g/day for 6 weeks

Other groups studied in this thesis are referred to as either:

a) Normal subjects. These are healthy volunteers who have no clinical evidence of any disease and who are not receiving any form of medical therapy other than was administered during studies.

b) Unselected duodenal ulcer patients. These are a group of patients with an endoscopically proven duodenal ulcer who were studied previously at the Royal Naval Hospital, Haslar under identical conditions, but who were not selected by criteria of nonresponse and, therefore, this group contains both responders and nonresponders.

c) Responder duodenal ulcer patients. These patients have had an endoscopically proven duodenal ulcer which has responded to

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treatment and no longer gives symptoms one month after stopping treatment. Most of this group had endoscopy performed to show healing, but this was not so in every case and therefore this group probably contained a small number of asymptomatic ulcers.

All duodenal ulcer patients studied in this thesis had no clinical evidence of any cardiac, respiratory, renal, hepatic, endocrine, neurological or other gastroenterological disease. Any patient with a concomitant gastric ulcer was excluded from the studies, as was any patient taking any form of medical therapy other than for his duodenal ulcer. Prior to each study, all ulcer medications were withdrawn for 24 hours.

Only male subjects and patients were studied because only one Nightingale Ward was available which was not equipped with facilities for both sexes. In addition, most of the personnel available as volunteers from Haslar were male subjects as were most of the Naval patients.

All patients and subjects gave their informed consent to all the studies in accordance with the Declaration of Helsinki. All studies were performed to a written protocol which had prior approval by the Royal Naval Hospital Ethical Committee.

2.2 Statistical Methods. All pH measurements have been converted to hydrogen ion (H^+) activity for statistical analysis.

Comparison of results was done by paired Student "t" test when looking at mean values in the same patients receiving different treatments and by unpaired "t" test when compairing mean values in different groups of patients receiving identical treatments.

All data was stored on a Hewlett Packard System 45 desk top computer, and all calculations performed by this computer after consultation with the statistics department of the Royal Naval Hospital, Haslar.

Data was judged to be significant if calculations showed findings to be of less than 5% probability ($p < 0.05$).

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2.3 The twenty-four hour study. The twenty-four study has been used as a standardised technique at Haslar since Pounder, Williams, Milton-Thompson and Misiewicz (1975) first used the method during the initial investigation of cimetidine. During their studies, they checked the reproducibility of the technique by using a placebo regimen on two separate occasions which resulted in a good correlation ($r=0.80$; $p<0.01$). The methods used since have been performed to an identical protocol.

Most studies in this thesis used a standard twenty-four hour protocol with different patients receiving a different treatment on each occasion. A minimum of one week was allowed between each study day. Patients fasted from midnight and attended a specially allocated ward at 0730. A size 10 French Salem sump nasogastric tube (Argyl Laboratories) was passed and position checked by water aspiration. Throughout the 24 hour period, pH was measured hourly using a glass electrode, previously calibrated with buffers of pH 4.0 and 7.0 before each batch of measurements.

The standard diet for each study day is shown in Table 2.1 and was estimated to contain approximately 2,960 calories, 144g of protein, 143g of fat, and 248g of carbohydrate. Patients were encouraged to lead a normal life, eat their meals at a table and entertain themselves with games such as cards, dominoes or watching television. The number of cigarettes and ad lib drinks were recorded on a data sheet and repeated on subsequent occasions by reference to the records.

At 0100 the stomach was emptied by manual suction and continuous mechanical aspiration at -50mm Hg used overnight to collect gastric secretion. Mechanical suction was interrupted by supplementary manual aspiration every 20 minutes and a small quantity of air blown down the tube to ensure patency.

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TABLE 2.

THE STANDARD DIET

0830	Breakfast	Cereal Gammon and Tomato Toast and Marmalade
1100	Coffee	
1300	Lunch	Roast Chicken and Sausage Vegetables Apple and Custard Tea
1600	Tea	
1930	Dinner	Grilled Steak Vegetables Jelly and Cream Tea
2200	Nightcap	Cheese and Biscuits Tea

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Overnight, volume of gastric secretion was recorded hourly and a 5ml sample of gastric juice taken for titration to pH 7.0 with 0.1 molar sodium hydroxide using an autoburette (Radiometer Copenhagen). From these readings, acid output was calculated.

All cimetidine tablets and injections and the intravenous impromidine were supplied by Smith, Kline and French Laboratories, Welwyn Garden, Herts; and ranitidine was supplied by Glaxo Group Research, Ware, Herts. All other drugs were supplied by the Pharmacy, RN Hospital, Haslar.

2.3.1 The effect of cimetidine 1g/day and 2g/day. Twelve nonresponders mean age 33 years (range 20-53) were studied over three separate 24 hour periods receiving either no treatment, cimetidine 200mg tds with food and 400mg nocte (1g/day) or cimetidine 400mg tds with food and 800mg nocte. Any sample of gastric juice taken within two hours of drug administration was returned to the stomach.

As the overnight period was of particular importance, passing the nasogastric tube was delayed until 1500. This allowed the patients to eat two of their three main meals without the inconvenience of a nasogastric tube. Otherwise the standard protocol as described in the preceding section was used. The basic design is shown in Figure 2.1. On attending the ward at 0730, a fasting serum was taken and stored at -20°C for later gastrin estimation using a radioimmune assay.

The nocte dose of cimetidine was adminstered at 2200. At 2130, a 19 gauge butterfly was inserted into a forearm vein and kept patent with heparinised saline. Blood was taken at 2130, 2200, 2230, 2300, 2330, 2400, 0100, 0200, 0400, and 0600, spun down at 5,000 revolutions per minute and the serum stored at -20°C for later estimation of serum cimetidine using high pressure liquid chromatography. This technique

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involves extracting the cimetidine using octanol. After a water-wash, back extraction into acid and salting out with sodium bicarbonate, the samples were injected as an alcoholic solution onto a Lycrosorb column using acetonitrile as a solvent. After approximately 20 minutes retention, cimetidine was detected at an ultraviolet range of 228-230 nm. The serum cimetidine results were compared to a previously reported study using eight healthy volunteers (Heading, Tothill, McLoughlin, Shearman, 1976.)

2.3.2 The effect of cimetidine in nonresponders compared with an unselected duodenal ulcer population. Dr. Richard Hunt kindly made available data from 25 duodenal ulcer patients who had been studied under an identical twenty-four hour protocol as the previous chapter. This group were not selected by criteria of nonresponse, but all had an endoscopically healed duodenal ulcer. To compare these previous results with nonresponders, it was decided to study a further 13 nonresponders over two separate 24 hour periods receiving either no treatment or cimetidine 1g/day. When combined with the results of the no treatment day and the cimetidine 1g/day study in the preceding section, a total of 25 nonresponders mean age 33 years (range 19-53) were available for comparison with the unselected duodenal ulcer patients.

It was felt at the start of this experiment that if any abnormal responses were observed, further investigation might include measuring overnight hormone levels. As a safety measure therefore, blood was taken at 2030, 2130, 2230, 2400, 0200, 0400, and 0600 via a 19 gauge butterfly cannula (previously inserted into a forearm vein) kept patent with heparinised saline. Before aspirating samples, 2mls. of blood were withdrawn and discarded in case heparin interfered with

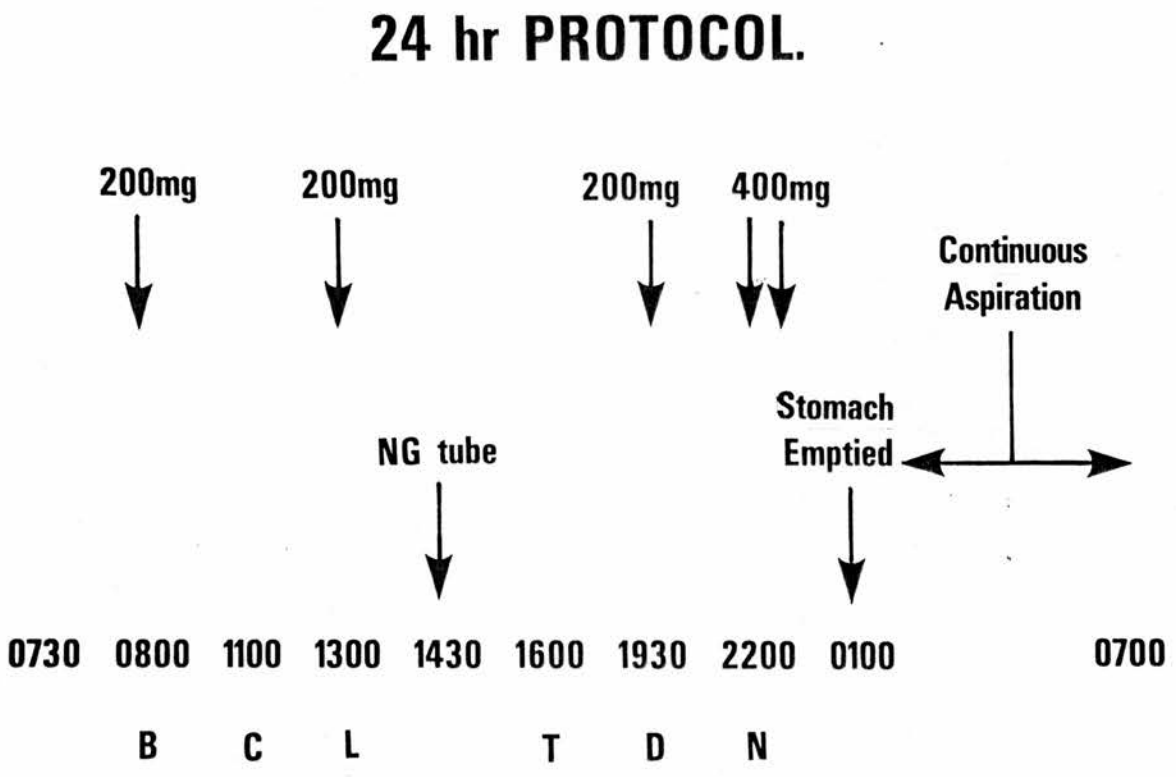

Figure 2.3.].

The twenty-four hour protocol - meals are represented by the letters beneath the time of day.

the hormone assay. In order to prevent inactivation of some hormones, blood was placed in a sequestrene tube prepared by the addition of trasylol. The samples were then spun down and the supernatant placed in a glass tube and immediately frozen at -20°C for storage.

2.3.3 The effect of cimetidine 1g/day combined with atropine 2.4mg/day. Eleven nonresponders mean age 32.1 years (range 20-45) and mean weight 73.3 kg (range 68-80) were studied over three separate 24 hour periods receiving either no treatment, cimetidine 1g/day or cimetidine 1g/day with atropine 2.4mg/day taken in four divided doses with food. Again, as the overnight period that was of particular interest, the nasogastric tube was passed at 1500. Otherwise, the protocol was as previously described in 2.3.1.

2.3.4 The effect of highly selective vagotomy. Ten nonresponders mean age 34.5 years (range 24-50) who had frequent severe relapses, not controlled by other medical measures were studies over two 24 hour periods receiving either no treatment or cimetidine 1g/day. Gastric juice was only sampled from 1500.

After the two study days, all the patients were referred for surgery and all had a highly selective vagotomy without complications. Six months post surgery, all had a history and examination, insulin test and repeat 24 hour study. The clinical assessment was to determine the Visik classification (Visik 1948), the insulin test to determine whether a complete vagotomy had been performed and the 24 hour study to compare the effect of surgery with that of cimetidine.

For the insulin test, patients fasted from midnight and attended the ward at 0730. A size 14 French Salem sump nasogastric tube (Shearman Laboratories) was passed and position checked by water aspiration. The stomach was emptied by manual suction and continuous

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mechanical aspiration performed at -50mm of mercury, supplemented by intermittent manual aspiration every 5 minutes to improve the accuracy of the collection technique (Baron 1978). Gastric secretion was collected every 10 minutes, volume measured, pH recorded and a 5ml sample titrated to pH 7 to calculate acid output. Samples were collected for a half-hour basal period and basal acid output expressed in mmol/hr after calculating the sum of the three ten minute values multiplied by two. A subcutaneous injection of insulin 0.2 units/kg was then given and gastric juice collected for a further 120 minutes. Peak acid output experessed in mmol/hr was calculated by the sum of the highest three consecutive ten minute collections multiplied by two.

CHAPTER 3

RESULTS

3.1 The effect of cimetidine 1g/day and cimetidine 2g/day. All patients tolerated the experiment well. Mean nocturnal hydrogen ion activity decreased from 45 mmol/l on no treatment to 33 mmol/l with cimetidine 1g/day ($p < 0.05$) and to 31 mmol/l with cimetidine 2g/day ($p < 0.05$ compared with no treatment and not significant compared with the 1g dose). Mean hourly variation is shown in Figure 3.1.1.

Mean nocturnal volume (Figure 3.1.2) decreased from 81ml/hr on no treatment to 64ml/hr with cimetidine 1g/day (not significant) and to 54ml/hr with cimetidine 2g/day (not significiant when compared with either no treatment or cimetidine 1g/day).

Mean nocturnal acid output (Figure 3.1.3) decreased by 41% with cimetidine 1g/day ($p < 0.05$) and by 51% with cimetidine 2g/day ($p < 0.05$ compared with no treatment and not significant compared with 1g dose).

Serum cimetidine levels are shown in Figure 3.1.4. Absorption of cimetidine in the nonresponders is no different from the normal subjects after a 400mg nocte dose. Doubling the dose of drug resulted in doubling of the peak serum level. Thus, despite adequate absorption, increasing the dose of cimetidine did not improve response.

3.2 The effect of cimetidine on nonresponders compared with an unselected duodenal ulcer population. All patients tolerated the study well. Mean nocturnal hydrogen ion activity is shown in Figure 3.2.1. On no treatment there was no signficant difference between the nonresponders and the unselected duodenal ulcer patients (49 mmol/l and 48 mmol/l respectively). After cimetidine 1g/day, mean nocturnal hydrogen ion activity decreased to 33 mmol/l in the nonresponders ($p < 0.05$) and to 12 mmol/l in the unselected duodenal ulcer patients ($p < 0.001$ compared with this group on no treatment and $p < 0.01$ compared with the nonresponders on cimetidine).

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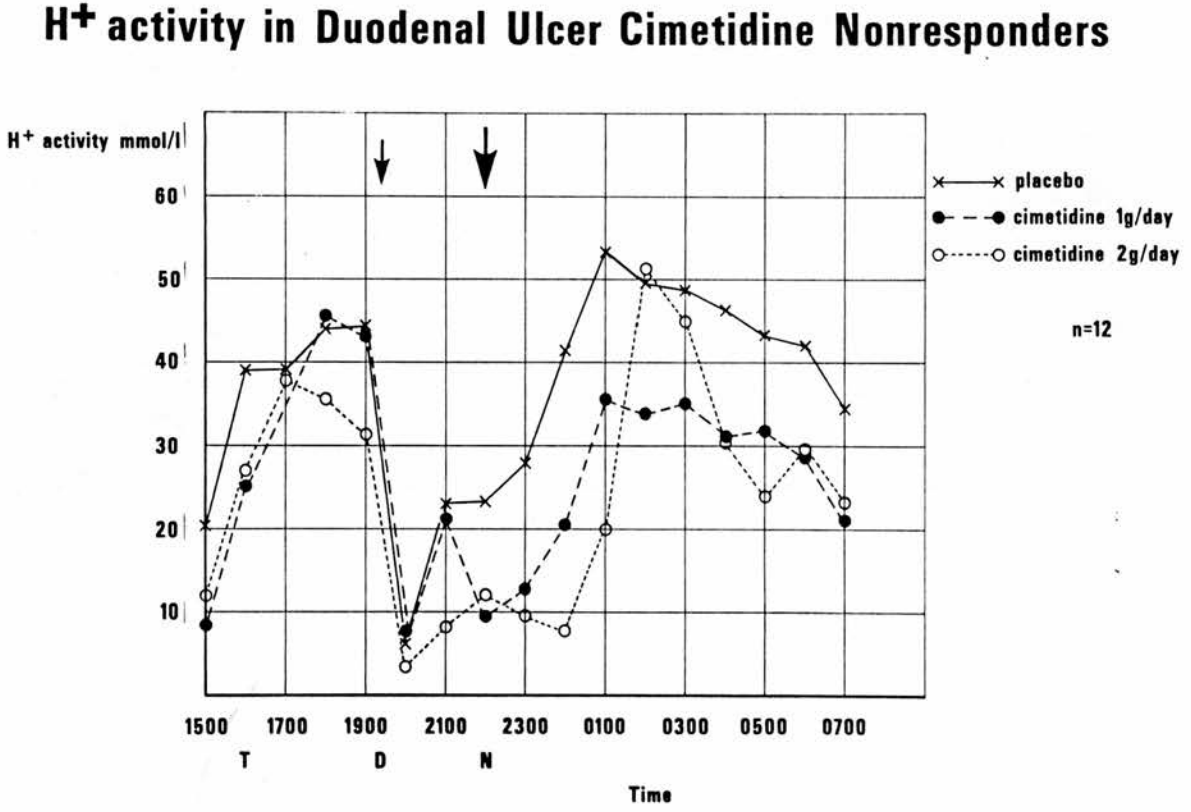
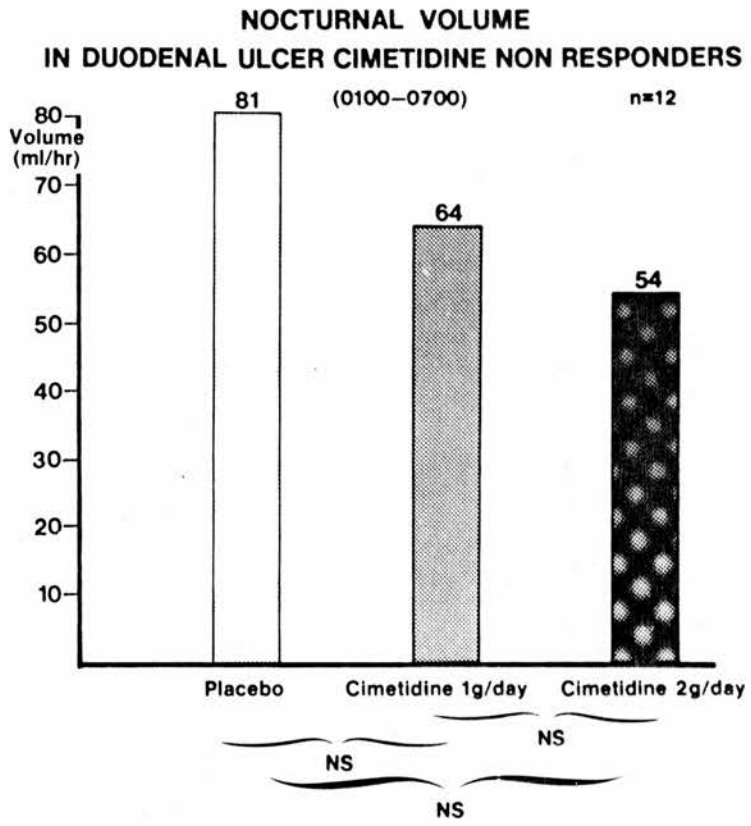


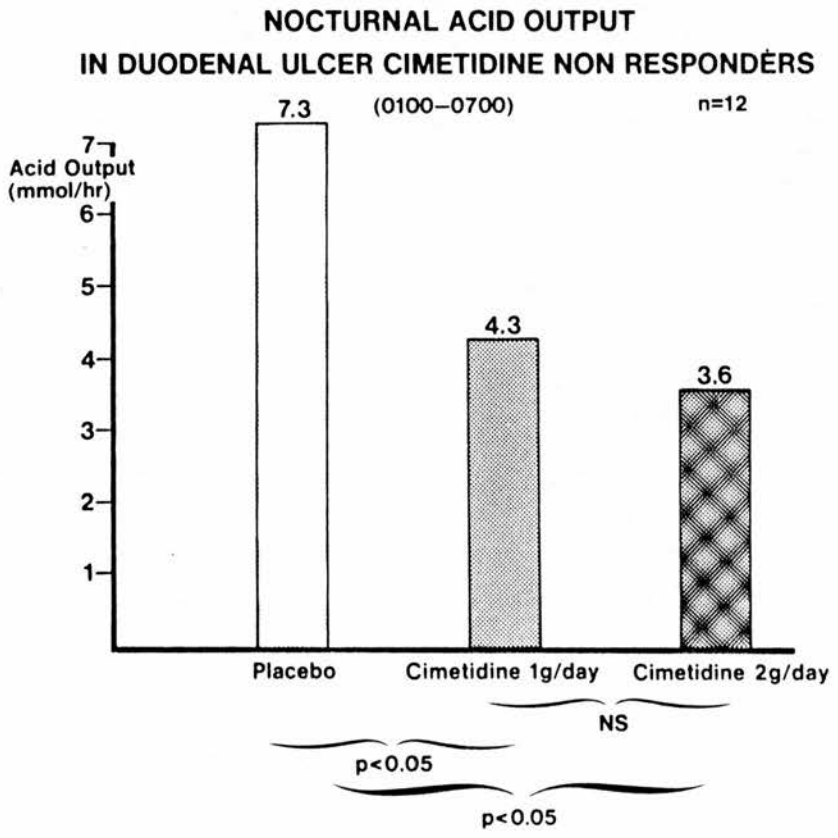
Figure 3.1.1

Mean hourly hydrogen ion activity



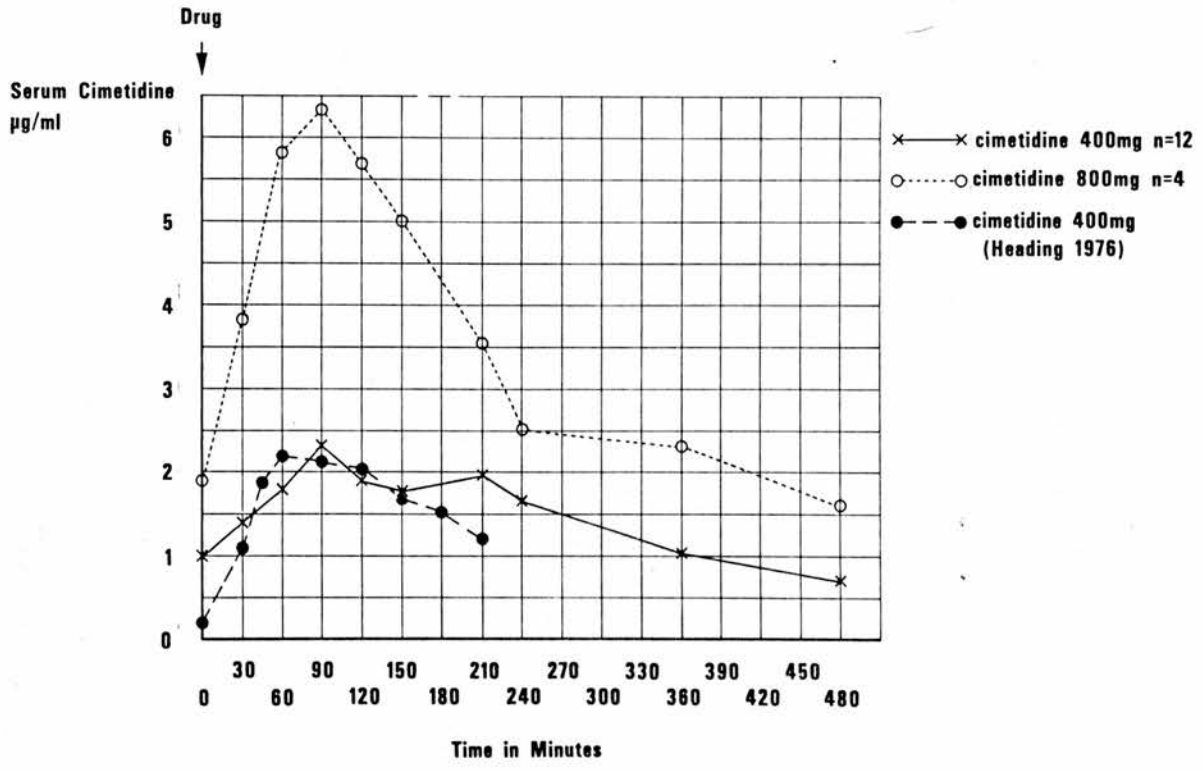
Mean Nocturnal Volume of Secretion

Figure 3.1.2



Mean Nocturnal Acid Output

Figure 3.1.3



Mean serum cimetidine levels in nonresponders after cimetidine 400 mg nocte, 800mg nocte, and in a previously reported group of normal subjects after cimetidine 400mg nocte

Figure 3.1.4

Volume of gastric secretion is shown in Figure 3.2.2. When on no treatment, there was no significant difference between the mean nocturnal volume of gastric secretion of the nonresponders and the unselected duodenal ulcer patients (74ml/hr and 55ml/hr respectively). After cimetidine 1g/day, volume decreased to 56ml/hr in the nonresponders (not significant) and to 29ml/hr in the unselected duodenal ulcer patients ($p< 0.01$ compared with the nonresponders on cimetidine.

Acid output is shown in Figure 3.2.3. There was no significant difference between the mean nocturnal acid output of the nonresponders and the unselected duodenal ulcer patients when on no treatment (6.6 mmol/hr and 4.3 mmol/hr respectively). After cimetidine 1g/day, acid output decreased to 3.5 mmol/hr in the nonresponders ($p< 0.05$) and to 0.68 mmol/hr in the unselected duodenal ulcer patients ($p< 0.001$ compared with this group on no treatment and $p< 0.01$ compared with the nonresponders on cimetidine).

Fasting serum gastrin was measured in 13 nonresponders - four of these had mildly elevated levels at 94, 92, 73 and 73 picog/l. The mean value for all thirteen was 58.2 picog/l (normal range 30-60).

Thus, nonresponse is associated with a decreased effect on acidity levels and acid output, and a total absence of any significant effect on the volume of gastric secretion during the overnight period and serum gastrin levels are not grossly abnormal.

3.3 The effect of cimetidine 1g/day combined with atropine 2.4mg/day.

All patients tolerated the experiment well although one subject complained of a dry mouth on the combination therapy.

Mean nocturnal hydrogen ion activity (Figure 3.3.1) decreased from 45 mmol/l on placebo to 31 mmol/hr on cimetidine ($p< 0.05$) and to 29 mmol/l on the combination ($p< 0.05$ compared with placebo and not

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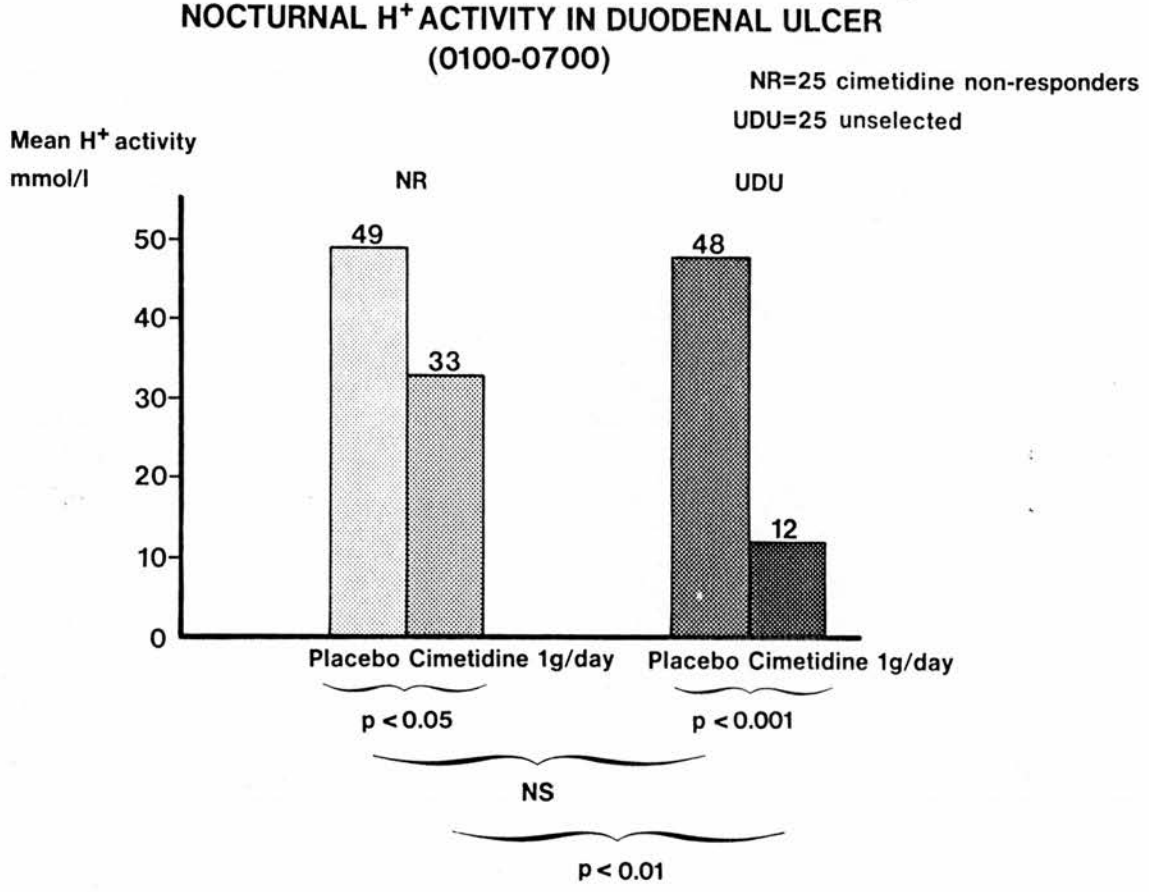
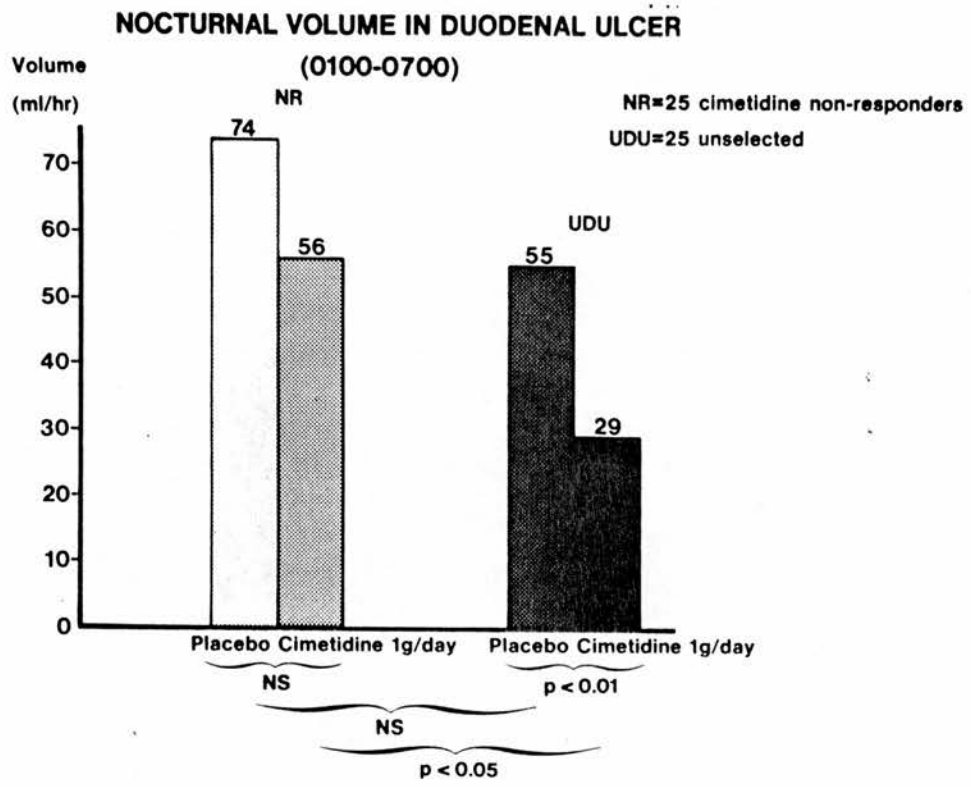


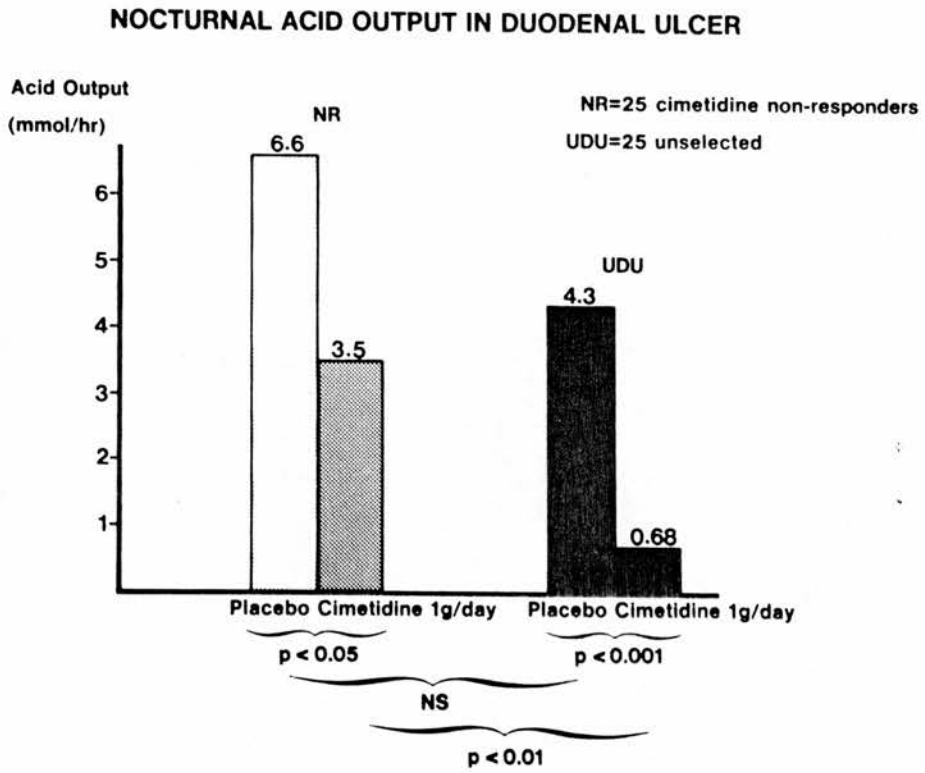
Mean Nocturnal Hydrogen Ion Activity

Figure 3.2.1



Mean Nocturnal Volume of Secretion

Figure 3.2.2



Mean Nocturnal Acid Output

Figure 3.2.3

significant compared with cimetidine alone).

Volume of gastric secretion decreased from 73ml/hr on placebo to 60ml/hr on cimetidine (NS) and to 52ml/hr on the combination (NS compared with placebo and NS compared with cimetidine alone). (Figure 3.3.2).

Mean nocturnal acid output is shown in Figure 3.3.4. On placebo, acid output was 7.3 mmol/hr compared to 4.3 mmol/hr after cimetidine ($p < 0.05$) and 3.6 mmol/hr after the combination ($p < 0.05$ compared with placebo and NS compared with cimetidine alone).

Thus, adding atropine 2·4mg/day does not improve response.

3.4 The effect of proximal gastric vagotomy. All subjects were graded Visik I or II post surgery and all had a complete vagotomy by all the previously reported criteria of : 1) No rise in acid concentration of 20mEq/l or 10mEq/l above basal concentration (Hollander 1946); 2) No rise of 0.25mEq in acid output in any hour (Stempien 1962); 3) Basal acid output of less than 2mEq/hr or no increase of more than 1mEq/hr (Bachrach 1962).

Mean nocturnal intragastric H^+ activity decreased from 41.1 $\pm$ 23.2 mmol/l on no treatment to 27.30 $\pm$ 35.38 mmol/l with cimetidine (NS) and to 14.47 $\pm$17.89 mmol/l six months after surgery ($p < 0.01$). Figure 3.4.1 shows the mean hourly values.

Volume of gastric secretion decreased from 43.6 $\pm$ 37.03 ml/hr on no treatment to 42.18 $\pm$ 25.95 ml/hr with cimetidine (NS) and to 17.62 $\pm$ 17.47 ml/hr six months after surgery ($p<0.05$ compared to cimetidine and $p < 0.01$ compared to no treatment). The results are expressed in Figure 3.4.2.

Acid output overnight decreased from 3.29 $\pm$ 3.06 mmol/hr on no treatment to 1.89 $\pm$ 2.08 mmol/hr with cimetidine ($p<0.05$) and to 0.95 $\pm$ 1.22 mmol/hr six months after surgery ($p < 0.05$ compared with cimetidine and $p < 0.01$ compared with the no treatment regimen). These results are shown in Figure 3.4.3.

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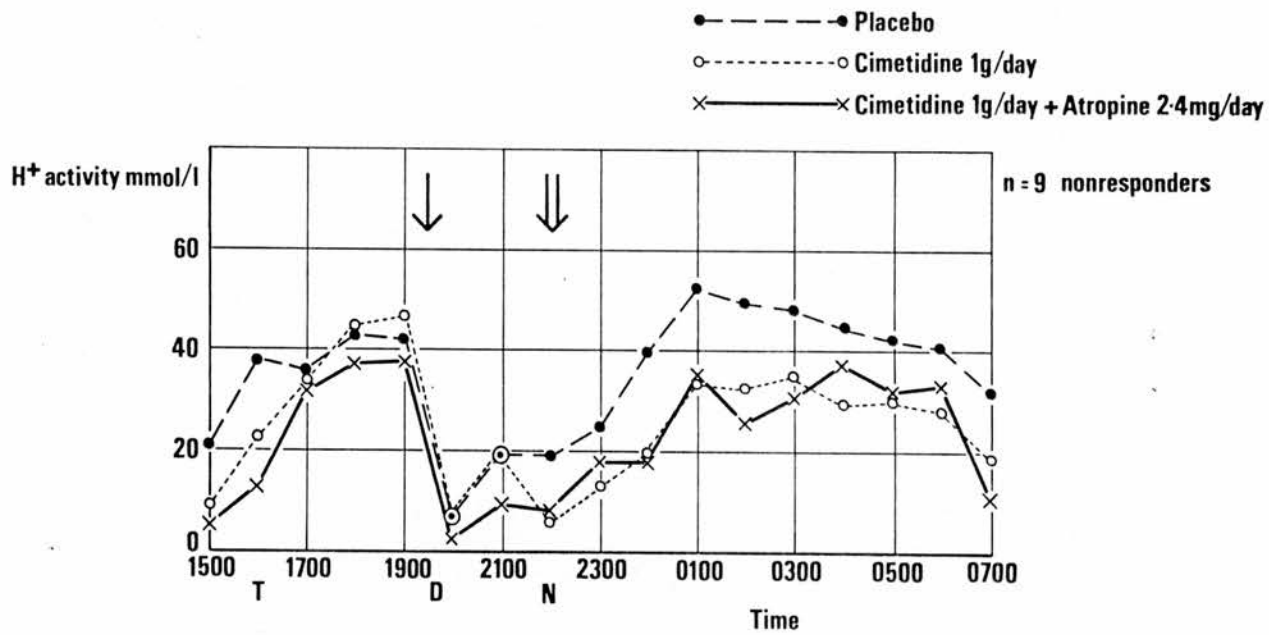
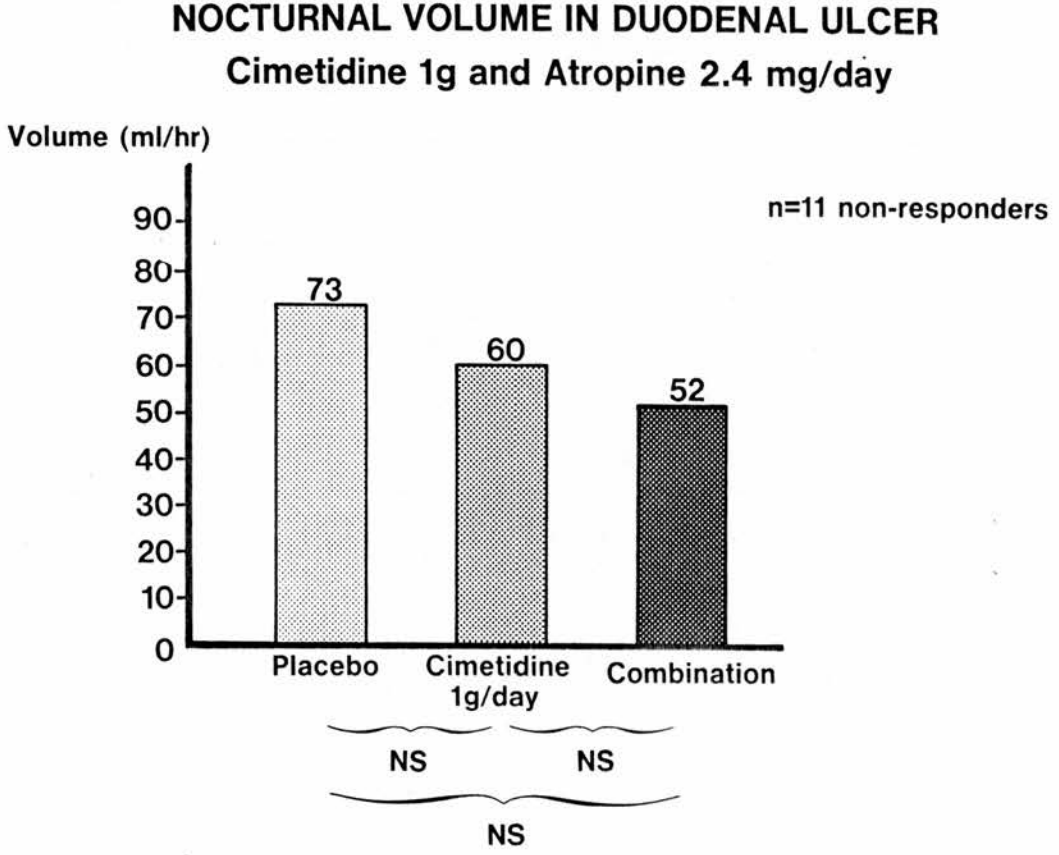
H^+ activity in Duodenal Ulcer after Cimetidine 1g and Atropine 2.4mg/day



Mean Hourly Nocturnal Hydrogen Ion Activity

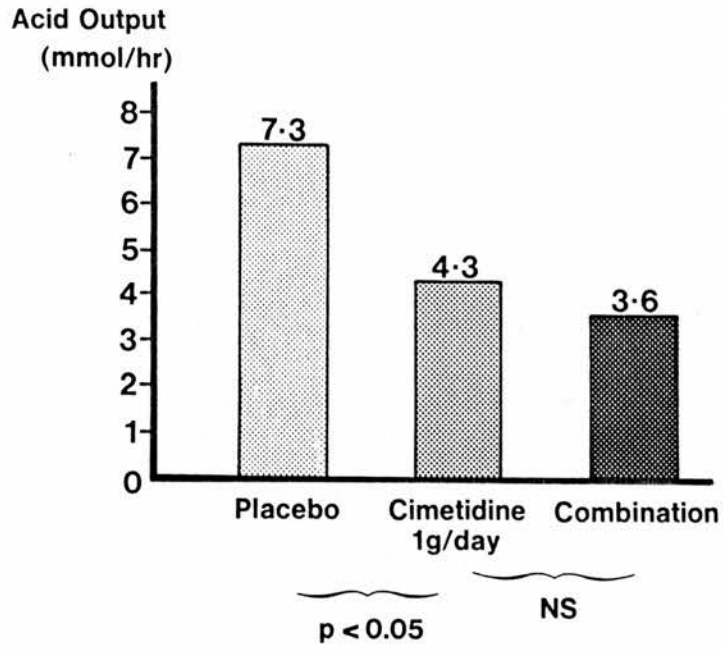
Figure 3.3.1



Mean Nocturnal Volume of Secretion

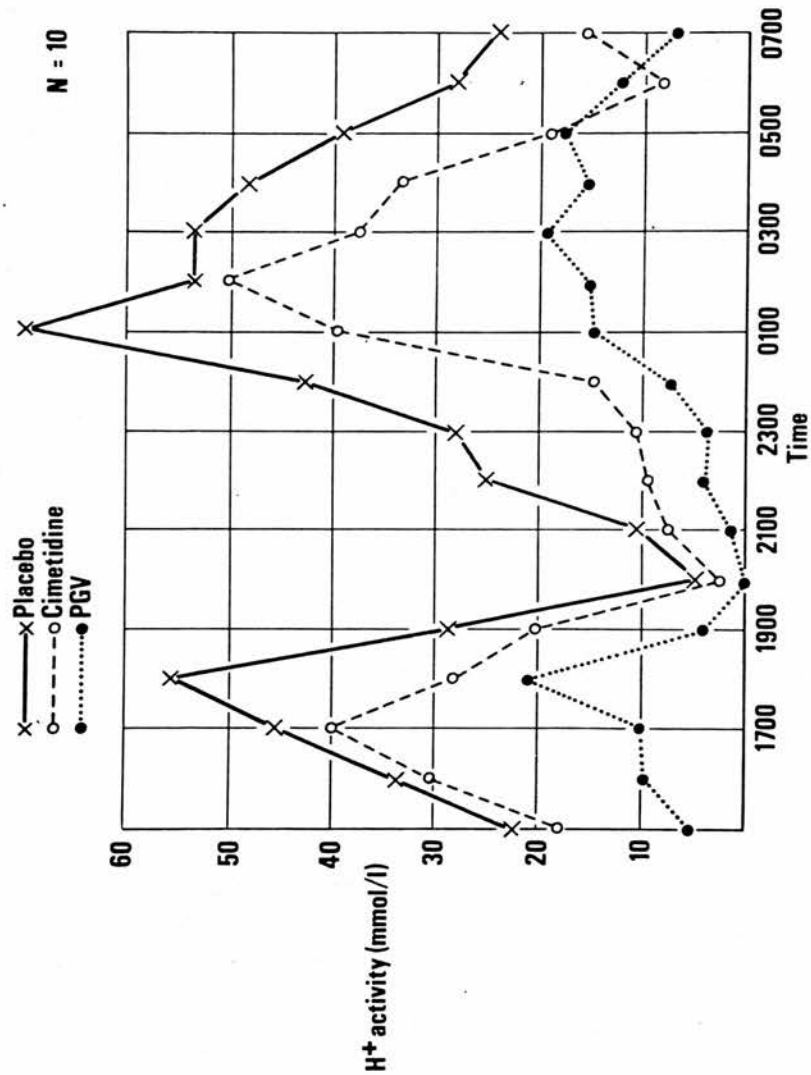
Figure 3.3.2

NOCTURNAL ACID OUTPUT IN DUODENAL ULCER
(0100-0700)
after Cimetidine 1g and Atropine 2.4 mg/day



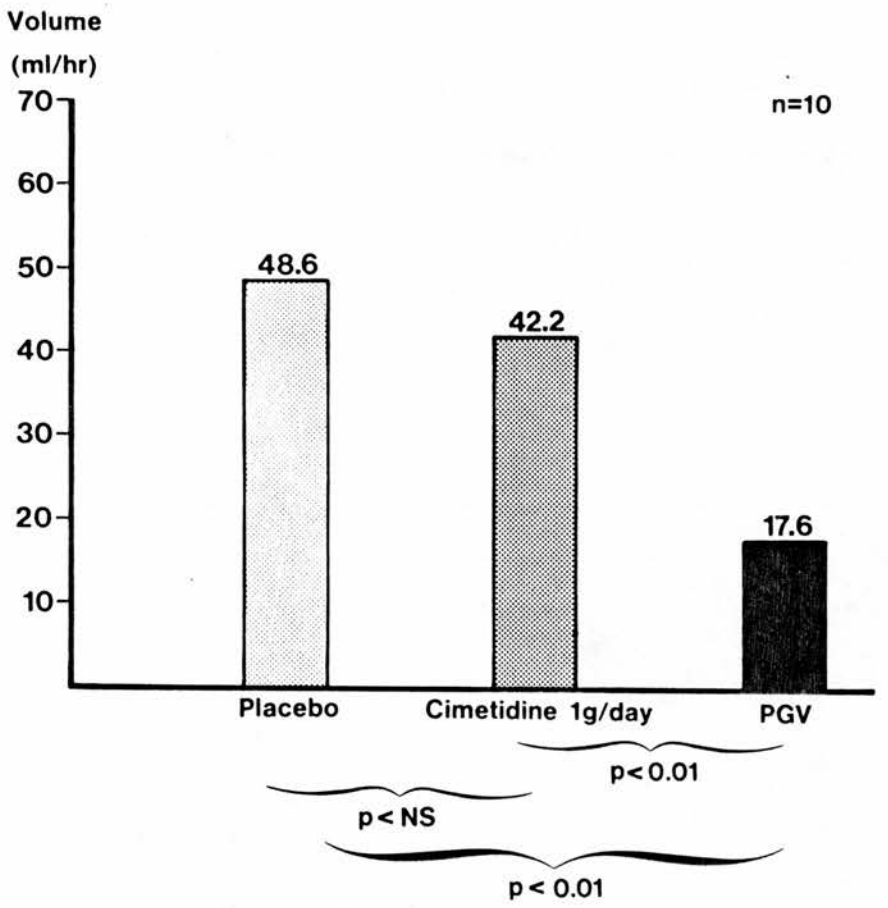
Mean Nocturnal Acid Output

Figure 3.3.3



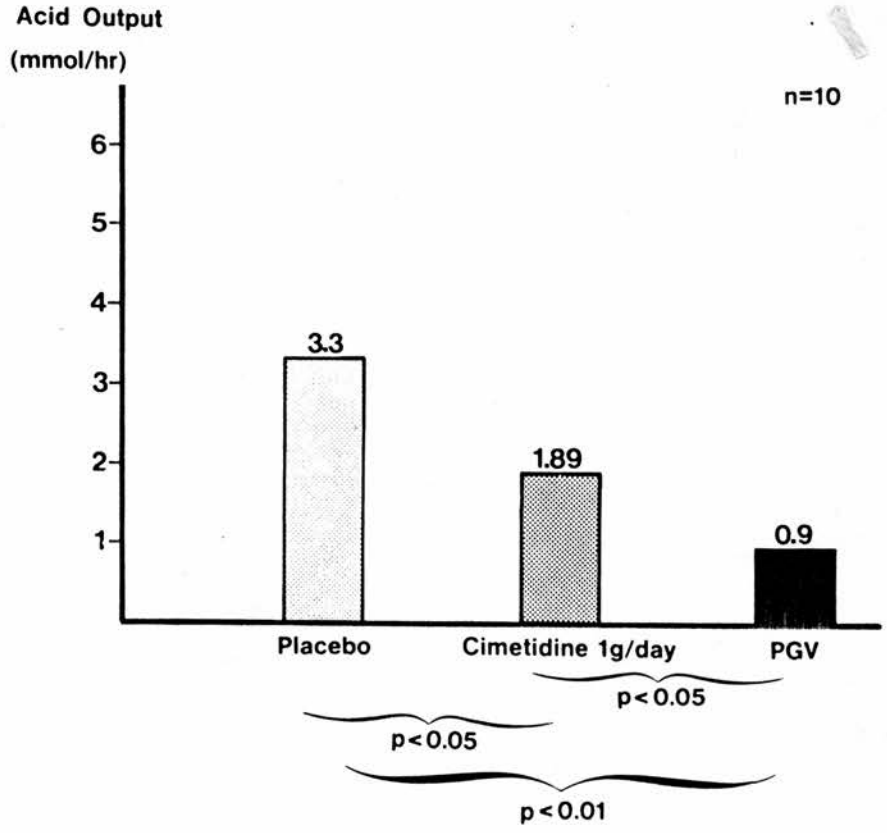
Mean Hourly Hydrogen Ion Activity After Vagotomy

Figure 3.4.1



Mean Nocturnal Volume in Nonresponders

Figure 3.4.2



Mean Nocturnal Acid Output in Nonresponders

Figure 3.4.3

These results show that in nonresponders, vagotomy is superior to cimetidine lg/day at decreasing intragastric acidity, volume of secretion and total acid output.

CHAPTER 4

DISCUSSION

4.1 The effect of cimetidine 1g/day and 2g/day. The aim of this study was to see if nonresponse was related to poor drug absorption and to assess whether increasing the dose of cimetidine would be expected to improve response. The results suggest that cimetidine is adequately absorbed in nonresponders and doubling the dose does not improve response despite a corresponding increase in peak serum level of drug.

The lack of benefit with larger dose agrees with a report that in duodenal ulcer patients, acid secretion is inhibited by a similar degree with either cimetidine 400mg nocte or cimetidine 800mg nocte (Blackwood and Northfield 1977). Similar healing rates are reported comparing 0.8mg/day with 1g/day (Peter, Fritsch, Nieschlag, Wienbeck and Strohmeyer, 1977; Kerr 1981), 1.2g/day (Blackwood, Maugdal, Pickard, Lawrence and Northfield 1976), 1.6g/day (Bodemar 1977; Blackwood, Maugdal, Pickard, Lawrence and Northfield 1976) and 2g/day (Bardhan 1981).

Binder, Cocco Crossley et al (1978) showed less complete acid inhibition with higher acid secretory rates. They hypothesised that higher doses of cimetidine may be necessary in patients with higher rates of acid secretion. Pounder, Williams, Hunt, Vincent, Milton-Thompson, Misiewicz (1977) found up to a maximum level, the degree of acid inhibition was closely related to cimetidine blood levels suggesting that poor acid control is associated with low serum drug levels. However, others have reported a poor correlation between drug levels and acid inhibition (Cohen, Siepler, Nation, Bombeck, Nyhus 1980) and that differences in clinical and endoscopic healing rates cannot be explained by differences in pharmacokinetics between patients (Webster, Petrie, Griffiths 1980). The results of this experiment would agree with this latter suggestion.

Although prolonging treatment with cimetidine, results in

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increasing the number of ulcers which heal (Bardhan 1980), increasing the dose of therapy is unlikely to increase the inhibition of acid secretion and will, therefore, probably not be of clinical benefit.

4.2 The effect of cimetidine on nonresponders compared to an unselected duodenal ulcer population. The aim of this study was to identify if nonresponders were different from other duodenal ulcer patients and compare their response to cimetidine.

The result demonstrates that nonresponders do not differ significantly from the unselested duodenal ulcer patients with regard to nocturnal acidity levels, acid output or volume of gastric secretion although the latter two parameters were slightly increased in the nonresponders.

Two previous reports have shown an increased basal acid output in cimetidine nonresponders (Cargil, Peden, Saunders, Wormsley 1978; Hetzel, Hansky, Shearman, Korman, Hecher, Taggart, Jackson, Gabb 1978), but both these reports were on fasted patients studied over a one hour period. This method of measuring basal acid output is unreliable (Baron 1980). One of the main problems is that it is never certain whether the stomach is fully emptied before collections start. Kirkpatrick and Hirschowitz (1980) noted a high residual volume in cimetidine nonresponders which they thought might be related to delayed gastric emptying. Thus, incomplete emptying of the stomach, which would give a falsely high value of basal acid output, is more likely if residual volume is large. Most other studies are in agreement that basal acid output in nonresponders is no different from other duodenal ulcer patients (Hunt 1981; Boyd, Wilson, Wormsley 1981; Bardhan 1981).

The present study suggests that serum gastrins are not grossly elevated in nonresponders. Although patients with Zollinger-Ellison syndrome relapse early after stopping cimetidine, and their symptoms are not always controlled by the recommended dose, this is an extremely

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rare form of nonresponse (Bianchi and Quatrini 1980).

The study also demonstrates that nonresponse is associated with a decreased effect of cimetidine at reducing nocturnal acidity and acid output together with a total abscence of any significant effect on the volume of gastric secretion in cimetidine nonresponders. These findings together with those showing adequate drug absorption in 3.1 , suggest that these patients are resistant to the pharmalogical effect of cimetidine and that noncompliance is unlikely to be a main cause of nonresponse as has already been demonstrated by Boyd, Wilson and Wormsley (1981). The decreased effect of cimetidine in reducing H^+activity has also been observed by Hunt (1981).

There are several explanations for these findings. Nonresponders might be at the poor response end of the normal therapeutic response curve, however, the observation of no significant reduction of volume of gastric secretion in contrast to the significant reduction in acid output and hydrogen ion activity suggest some other mechanism is involved.

One hypothesis is that cimetidine can only decrease acid secretion by a defined amount in individual patients. However, although H^+ activity, acid output and volume were similar in the two groups on no treatment, after cimetidine, decreases of hydrogen ion activity, acid output and volume in the unselected duodenal ulcer patients were all much greater than the decreases in the nonresponders.

Duodenal ulcer may be the result of increased vagal drive (Dragstedt 1945) and Fritsch, Scholten, Muller and Hengels (1980) have shown that the more acid secretion is sensitive to vagal stimulation, the less the effect of histamine H2-receptor antagonists. Many of the cimetidine nonresponders might have relapsed early and the

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observations may have been made on disease activity. This is difficult to disprove unless weekly endoscopy is performed which is obviously not practicable. At the start of the studies, all patients were in remission and if the observations are related to disease activity, cimetidine would be unlikely to promote ulcer healing in any patients.

Another explanation for the observation of lack of effect on volume is that collection techniques were poor in the nonresponders. The techniques certainly have limitations but they were no different from those used for the unselected duodenal ulcer patients, and any inaccuracies should have balanced out. The techniques have not been changed at Haslar since the original studies by Pounder, Williams, Milton-Thompson and Misiewicz (1975), all of which showed cimetidine to decrease volume of gastric secretion in other duodenal ulcer patients. The present experiment was conducted alongside other studies (Gledhill, Mills, Clancy, Buck, Hunt, Burland 1982) which used the same collection techniques yet demonstrated a reduction in volume with cimetidine. Residual volume has been reported to be increased in cimetidine nonresponders (Kirkpatrick and Hirschowitz 1980) and it is possible that the stomach was not emptied properly before overnight collections were started. If this were true, nonresponders would have been expected to have increased volume of secretion when reciving no treatment compared to the unselected duodenal ulcer patients, and this we did not observe. In addition, great care was taken to ensure the stomach was properly emptied before overnight collections.

Cimetidine may increase reflux and may have explained the lack of effect on volume. Few samples however were noted to be bile stained and if reflux had increased, the lack of effect on volume should have also been noted in the unselected duodenal ulcer patients. It may have been that reflux increases with cimetidine only in nonresponders.

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This might be a reason for nonresponse in gastric ulcer, but it is unlikely to be a cause of nonresponse in duodenal ulcer.

A further explanation for the lack of effect on volume is that cimetidine may have no effect on cholinergic pathways in nonresponders. The review of the literature in the introductory chapter points to increased vagal drive as a cause of nonresponse but if this were the case, nonresponders should have increased volume of gastric secretion when receiving no treatment. However, although a slight increase was observed. this was not significant. The other possibility is that cimetidine causes increased vagal drive. For this to occur, a hypothesis must be made that histamine inhibits vagal tone and treatment with an H2-receptor antagonist stops vagal inhibition. This theory is supported by the findings of Maybury and Carr-Locke (1980) who found that cimetidine had no effect on insulin induced acid secretion in patients who were resistant to cimetidine treatment.

If increased vagal drive leads to nonresponse, acid should be controlled better by combining cimetidine with an anticholinergic agent. The next study, therefore, measured the effect of cimetidine combined with atropine 2.4mg/day on acid secretion in nonresponders.

4.2.3 The effect of cimetidine 1g/day in combination with atropine 2.4mg/day. This study demonstrated that cimetidine had a decreased effect on nocturnal hydrogen ion activity and acid output but no significant effect on volume of gastric secretion. The addition of atropine gave no added benefit. Volume of gastric secretion is thought to be predominantly under cholinergic control (Kirkpatrick, Hirschowitz 1980) and, therefore, adding an anticholinergic agent would seem a reasonable idea. Other authors have suggested combining cimetidine with anticholinergics (Thompson, Albinus, Blair, Reed, Venables, 1975).

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Previous reports on combination therapy are variable. Pounder, Hunt, Vincent, Milton-Thompson and Misiewicz (1977) found no additional benefit from atropine 2.4mg/day and Blackwood and Northfield (1977) found adding poldine did not improve response. Thjodleifsson and Wormsley (1974) and Barbezat and Bank (1976) suggested adding atropine provided better control of acid secretion, and Venables (1980) suggested benefit by adding poldine. Londong, Londong, Weber and VanWerder (1980) also found improved response from adding pirenzepine.

The addition of an anticholinergic agent therefore does not always improve control of acid secretion. To investigate vagal tone further, the next study measured acid secretion in nonresponders after proximal gastric vagotomy.

4.2.4 Proximal Gastric Vagotomy. The result repeated the earlier finding that cimetidine had no significant effect on volume of gastric secretion in cimetidine nonresponders. However, vagotomy produced significantly better decreases in nocturnal hydrogen ion activity, acid output and volume compared with cimetidine.

The result agrees with Hunt, Vincent, Kelly, Perry, Milton-Thompson (1980) who found vagotomy decreased hydrogen ion activity better than cimetidine in cimetidine resistant patients. Pounder, Williams, Hunt, Vincent, Milton-Thompson and Misiewicz (1977) however, found vagotomy produced an equal decrease in hydrogen ion activity to that produced by cimetidine but they studied unselected duodenal ulcer patients who were not classified as being cimetidine responder or nonresponder.

Although cimetidine has resulted in a decline in the number of elective operations for duodenal ulcer (Venables 1981); Bardhan and Hinchcliffe 1981; Venables 1980; Hunt 1981; Wyllie, Clark, Alexander-Williams, Bell, Kennedy, Kirk and McKay 1981; Goggan, Lambert and Langman 1981), there have been reports of cimetidine either not

affecting or increasing the number of operations for perforated ulcer (Price and Elder 1981; McKay and McArdle 1981). Indications for surgery are failed medical treatment with severe, frequent attacks or complications such as haemorrhage, perforation and pyloric stenosis. Contraindications remain as mild or infrequent attacks, other disease or bad anaesthetic risk. Cimetidine has not altered these indications and, therefore, failure to respond to H_2 blockade is not necessarily an indication for surgery although patients who continue to meet criteria of nonresponse should be offered surgery.

One question which needs to be answered is "will vagotomy cure the cimetidine failures, or is more radical surgery required"? The results suggest that proximal gastric vagotomy should result in a low relapse rate compared to cimetidine. Some reports suggest that nonresponders do badly with vagotomy while others recommend this form of surgery (Venables 1980; Valleur, Adam, Alasseur, Bitoun, Hautefeuille 1979; McWhinnie, Gray, Smith, Gillespie 1980; Bardhan 1981; Blackett and Johnston 1981). What are the reasons for these differences? Blackett and Johnston 1981) report a 16% recurrence rate after highly selective vagotomy both before and after the introduction of cimetidine. Venables (1980) thought that 16.6% recurrence rate after highly selective vagotomy in nonresponders was cause for concern, particularly when compared with a 2% two year recurrence rate before cimetidine. A recent review (Gillespie 1982) found a 15-20% recurrence rate with proximal gastric vagotomy, and it may well be that high recurrence rates are associated with proximal gastric vagotomy rather than cimetidine failures. Recurrence rates are usually judged endoscopically whereas before cimetidine, such a strict method of assessment was rarely available. The silent ulcer is now a well recognised entity in endoscopic clinical trials. Vagotomy results in division of both sensory and secretory

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nerves, which, before endoscopy, might have resulted in a large number of silent ulcers after surgery, thus giving falsely low relapse rates.

Surgery is perhaps more effective at providing long term relief of symptoms, but is a high price to pay if attacks have been infrequent. Cimetidine is probably slightly less expensive than surgery (Pounder 1981; Venables 1981) and has no mortality. Long term side effects with cimetidine remain unknown and although surgery is well tried, one report (Stalsberg and Taksdal 1971) has shown a sixfold increase in the risk of gastric carcinoma in the gastric remnant following gastrectomy which could be attributed to prolonged achlorhydria.

Although there are disadvantages to both cimetidine and surgery, if the latter is indicated, this study suggests nonresponders should do as well as other duodenal ulcer patients, irrespective of their response to H2 blockade. Nonresponse, therefore, is not an indication for more radical surgery.

The results so far are contradictory in that although vagotomy was more effective than cimetidine alone, adding atropine 2.4 mg/day, which should inhibit vagal drive, provided no additional effect. It was therefore decided to look at vagal function further.

Pepsin secretion is mainly a result of vagal stimulation (Venables, Wheldon, Johnston 1975; Venables and Johnston 1969; Wilson, Dymock and Cowley 1974; Berstad, Peterson, Roland and Liavig 1973) and , therefore, to investigate cholinergic stimuli in more detail, it was decided to measure the effect of cimetidine on nucturnal pepsin secretion.

PART II

PEPSIN

CHAPTER 5

METHODS

5.1 The effect of cimetidine on nocturnal pepsin secretion. The previous experiments have all suggested that nonresponse may be due to increased vagal drive. Pepsin is released after cholinergic stimuli and it was, therefore, decided to measure the effect of cimetidine on nocturnal pepsin secretion in a group composed of 12 nonresponders and 6 responder duodenal ulcer patients.

Pepsin is usually measured at pH2 by acting on haemoglobin or albumin to release tyrosine which can be read at 280nm or measured by reaction with folin phenol reagent. Both methods require separation of the substrate and products before analysis can be completed. The activity of pepsin is then compared against hog pepsin preparations which are variable purity and potency.

Gray and Billings (1982) have described a technique of measuring peptic activity which offers advantages over previous methods. They devised a substrate consisting of an albumin-bromphenol blue complex which is attacked at pH 2.0 to release the dye in a reaction which follows zero order kinetics. The system was developed into an automated kinetic assay which eliminated the necessity of separating unchanged substrate from the released product.

The analysis is carried out on a COBAS centrifugal analyser which calculates the best regression line and presents the results in international units. The substrate is made up by taking 3ml of Bromphenol Blue (1.0mmol/l) dissolved in the minimum amount of ethanol, made up with pH 2.0, 0.4 molar glycine-hydrocholoric acid buffer and adding 1.8ml of bovine albumin (Sigma) 10g/100ml. The resulting solution is made up to 20ml with glycine buffer. Gastric juice is added to this substrate in a reagent boat of a Cobas analyser and enzyme activity monitored at 605 nm. over a period of five minutes. The period of zero-order kinetics is used to determine the absorbance change per minute from which peptic activity is calculated in international units per litre.

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Gastric juice was taken from six normal subjects after intramuscular pentagastrin 6µg/kg and used to compare the method of Gray and Billings with that of Berstad (1970).

Some of the advantages of this pepsin assay are: standardisation of the method , expression of the peptic activity in international units, easily made and stable reagent, substrate and products do not require separation, and finally the whole analysis is carried out on an automatic analyser with its attendant advantage of high throughput and minimal operator involvement.

Twleve nonresponders mean age 34 years (range 20-53) and six responders, mean age 31.3 years (range 22-48) were studied over two 24 hour periods receiving either no treatment or cimetidine in standard dose. The protocol was identical to that described in 2.3.1, but in addition to taking a sample of gastric juice to calculate acid output, a 5ml sample was immediately frozen at -20°C and stored the following day at -90°C for later estimation of peptic activity.

When the results of peptic activity became available, concentration was multiplied by volume to obtain a value of pepsin output.

5.2 The effect of ranitidine on nocturnal acid and pepsin output. Six nonresponders, mean age 32.5 years (range 20-36) were studied over three 24 hour periods receiving either no treatment, cimetidine 400mg b.d. or ranitidine 150mg bd. The dose of cimetidine was different from the previous experiments because of the change in recommended dose (Burland, Brunet, Hunt, Melvin, Mills, Vincent, Milton-Thompson 1980; Kerr 1981; Eckardt 1981). The study was also designed to compare the new cimetidine dose with the twice daily ranitidine regime at decreasing 24 hour intragastric acidity. For this reason, the nasogastric tube was passed at 0730 and data collected for the whole 24 hour period.

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Overnight, volume of secretion was recorded and 5ml samples taken hourly for pH estimation followed by titration to pH 7, and for immediate freezing at -20°C followed by storage at -90°C for later pepsin estimation.

5.3 The effect of impromidine on pepsin secretion in normal subject.

Ten healthy volunteers (mean age 26 years, mean weight 73kg) fasted from midnight and attended the ward at 0730. A size 14 French Salem sump nasogastric tube (Shearman Laboratories) was passed and position checked by water aspiration. The stomach was emptied by hand suction, the subject placed supine and the nasogastric tube connected to a pump for continuous mechanical aspiration at -50mm mercury.

Samples of gastric juice were taken every 10 minutes throughout the study, volume and pH recorded and a 5ml sample titrated to pH 7.0 with 0.1 sodium hydroxide to calculate acid output. A second 5ml sample was immediately frozen at -20°C and stored at -90°C for later pepsin estimation.

Continuous suction was interrupted every 5 minutes by manual syringe aspiration to ensure more accurate collection (Baron 1978). Samples were taken over a 90 minute basal period and basal acid and pepsin outputs calculated by the sum of the last six 10 minute collections. A 19 gauge butterfly cannula was then inserted into a forearm vein and an intravenous infusion of impromidine 10µg/kg started. Samples were collected for a further 90 minutes, after which, the subjects were given food. Peak acid and pepsin outputs were calculated from the sum of the last six 10 minute collections.

5.4 The effect of cimetidine on overnight serum glucose and insulin.

The serum samples obtained from six patients in study 2.3.2 were transported in cardice to Dr.David Saunders at the Department of Physiology, Newcastle Medical School who kindly agreed to measure serum glucose

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and serum insulin on the no treatment and cimetidine regimens.

5.5 The effect of cimetidine 1g/day combined with atropine 4.8mg/day.

Seven nonresponders mean age 31.3 years (range 20-39), mean weight 75.4 kg (range 67.3-81.8) were studied over four separate 24 hour periods receiving either no treatment, cimetidine 400mg bd., atropine 4.8mg/day or a combination of the cimetidine and atropine. Both drugs were taken with food, the atropine being given in four divided doses. Otherwise the protocol was as in 5.2.

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CHAPTER 6

RESULTS

6.1 The effect of cimetidine on nocturnal pepsin output. The correlation of the method of Gray and Billings with that of Berstad using juice obtained from six pentagastrin tests in normal subjects is shown in Figure 6.1.1 (r=0.984).

Mean nocturnal (0100-0700) acid and pepsin output for all the duodenal ulcer patients receiving the two treatments are shown in Figure 6.1.2. Nocturnal pepsin output increased from 1.55 ± 2.74 IU/hr on no treatment to 3.88 ± 5.17 IU/hr on cimetidine while acid output decreased from 5.64 ±4.49mmol/hr on no treatment to 3.71 ± 3.27 mmol/hr on cimetidine. The increase in pepsin output was significant at the 5% level and the decrease in acid output significant at the 1% level.

Table 6.1 shows the effect of cimetidine in the two groups of responders and nonresponders. It can be seen that the highest mean pepsin output was in the nonresponder group when receiving cimetidine. The standard deviations were large, the number of patients small and, therefore, the result was not significant.

The responder patients decreased their acid output from 5.10 mmol/hr to 1.20 mmol/hr, but the nonresponders decreased acid output from 5.93mmol/hr to 3.83mmol/hr with cimetidine.

The relationship between acid and pepsin output showed no correlation on no treatment (r=0.04 NS), but on cimetidine the correlation became highly significant (r=0.64, $p < 0.0001$). The mean hourly values of acid and pepsin output in four patients chosen at random are shown in Figure 6.1.3. The increased correlation with cimetidine can be clearly seen.

6.2 The effect of rantidine. All patients tolerated this study well. Mean 24 hour hydrogen ion activity decreased from 34.49 ± 22.87 mmol/l on placebo to 23.67 ± 20.12 with cimetidine ($p < 0.05$) and to 12.85 ± 18.31 with ranitidine ($p < 0.01$ compared with placebo treatment and

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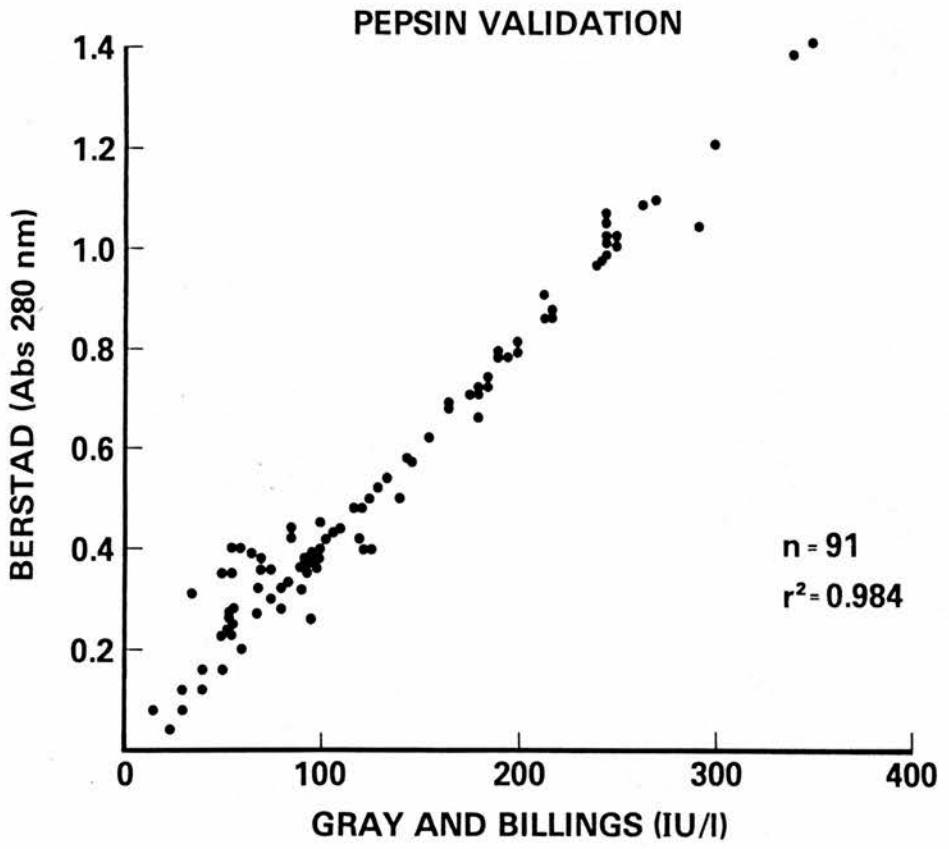
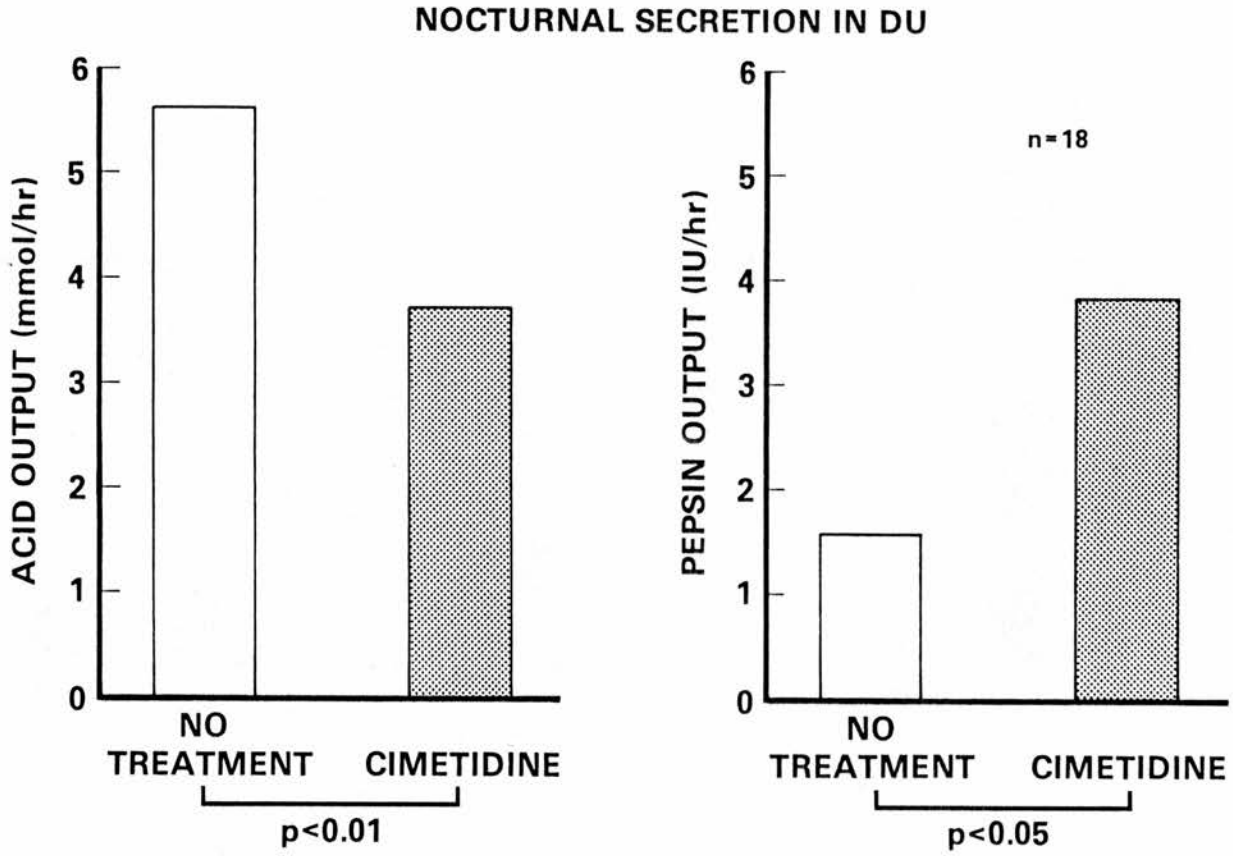


Correlation of Gray and Billings with Berstad

Figure 6.1.1

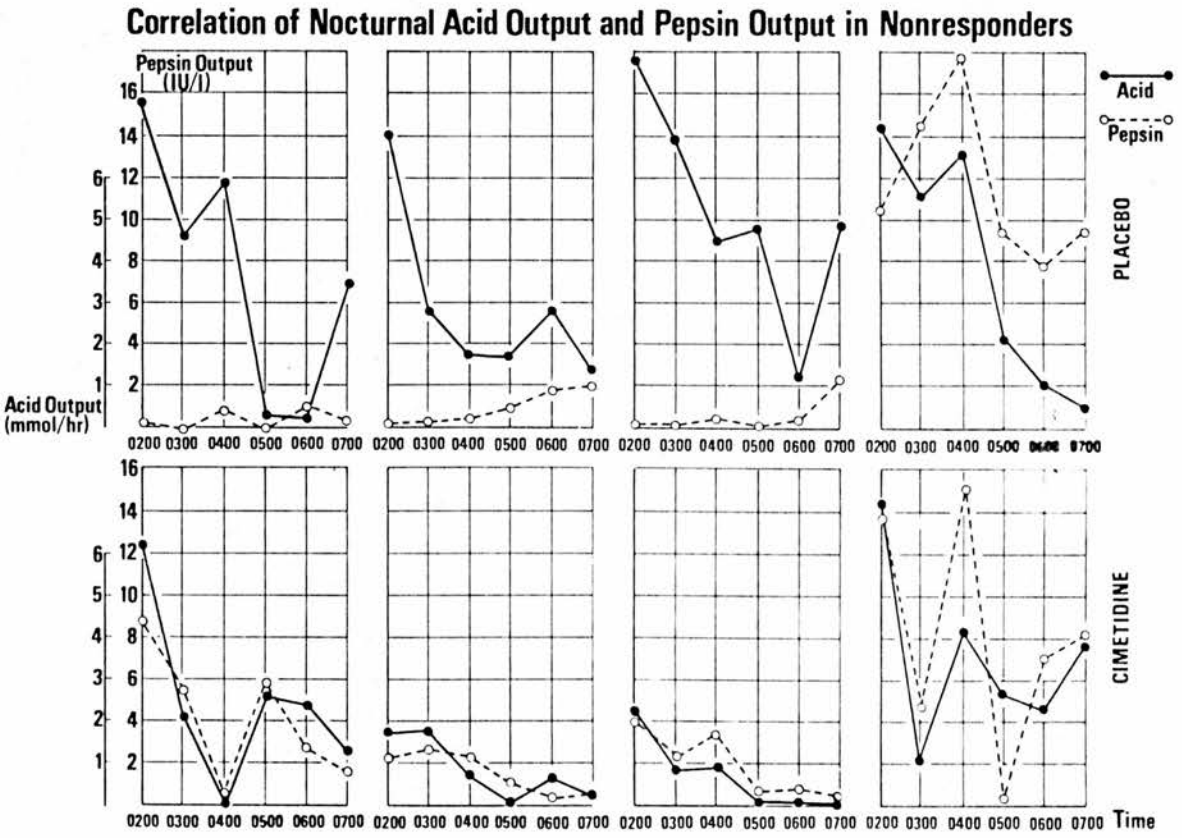


Mean Nocturnal Acid and Pepsin Output

Figure 6.1.2

TABLE 6.1.

	ACID OUTPUT (mmol/hr)		PEPSIN OUTPUT (IU/hr)	
	No Treatment	Cimetidine	No treatment	Cimetidine
NONRESPONDERS	5.93 ± 5.08	3.83 ± 3.83	2.1 ± 3.2	4.8 ± 5.14
RESPONDERS	5.1 ± 2.9	1.2 ± 0.93	0.43± 0.25	2.8 ± 1.63



Correlation of Nocturnal Acid Output and Pepsin Output in Nonresponders

Figure 6.1.3

and $p < 0.05$ compared with cimetidine).

Mean nocturnal hydrogen ion activity (Figure 6.2.1) decreased from 44.46 ± 15.97 mmol/l on placebo to 24.78 ± 19.06mmol/l with cimetidine (NS) and to 23.2 ± 19.74 with ranitidine ($p < 0.01$ compared with placebo and NS compared with cimetidine).

Nocturnal volume of gastric secretion (Figure 6.2.2) decreased from 57.64 ± 37.79ml/hr on placebo to 54.97 ± 29.85ml/hr on cimetidine (NS) and to 34.53 ± 19.27 on ranitidine (NS compared with placebo and NS compared with cimetidine).

Mean nocturnal acid output (Figure 6.2.3) decreased from 5.19 ± 4.13mmol/hr on placebo to 3.79 ± 2.98mmol.hr on cimetidine (NS) and to 1.67 ± 1.82mm91/hr on ranitidine ($p < 0.05$ compared with placebo and $p < 0.05$ compared with cimetidine).

Mean nocturnal pepsin output is shown in Figure 6.2.4 . On no treatment, pepsin output was 1.6 ± 1.88 IU/hr compared to 2.9 ± 3.2 IU/hr on cimetidine and 3.12 ±2.14 IU/hr on ranitidine.

Although the numbers are small, these results suggest ranitidine is not significantly better than cimetidine at decreasing nocturnal H^+ activity or volume of secretion and that ranitidine also stimulates pepsin output.

6.3. Impromidine in normal subjects. All subjects tolerated the study well. Acid and pepsin output are shown in Figure 6.3.1. Mean basal acid output was 4.11 ± 3.88mmol/hr which rose to 29.72 ± 8.2 mmol/hr with impromidine ($p < 0.001$). Mean basal pepsin output was 3.65 ± 3.63 IU/hr which decreased to 0.21 ± 0.18 IU/hr with impromidine ($p < 0.02$). The decrease in pepsin output was noted in every subject. Even in the first 30 minutes of impromidine infusion, mean pepsin output decreased to 0.8IU/hr which suggests that this decrease is a true decrease in secretion and not a "washout phenomenon".

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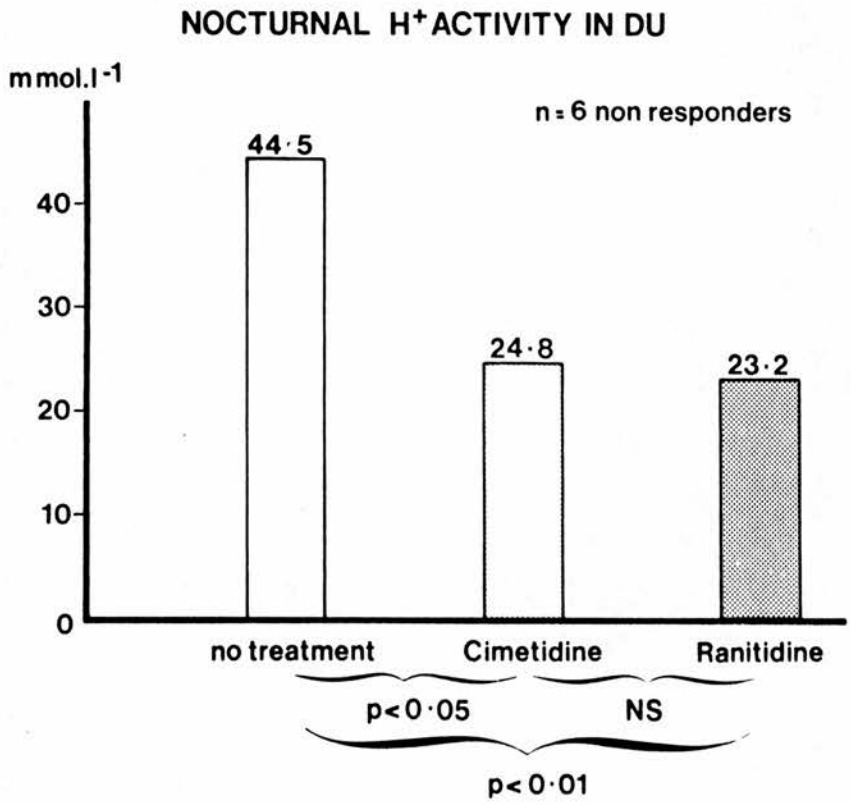
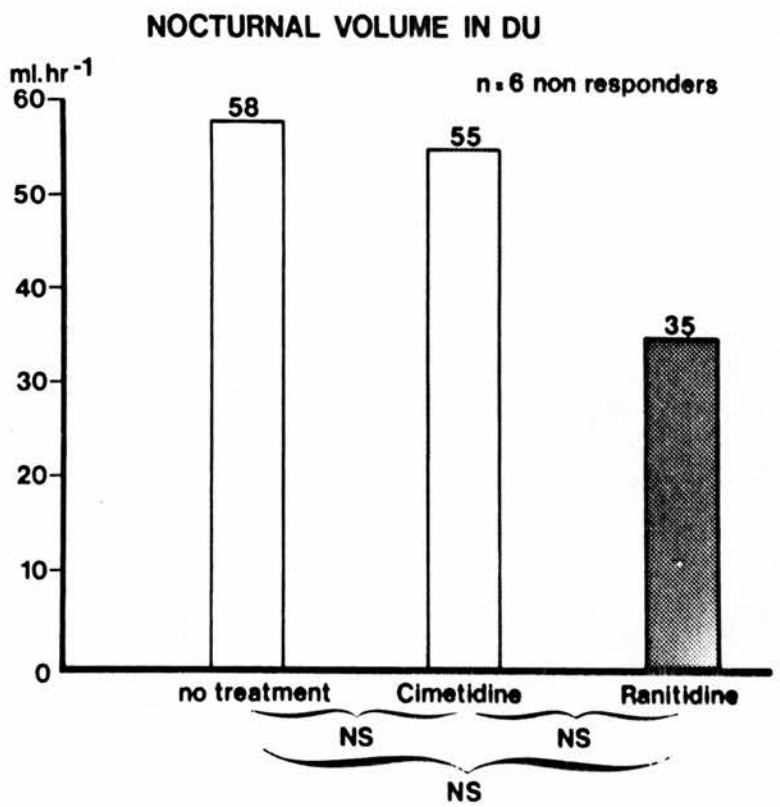


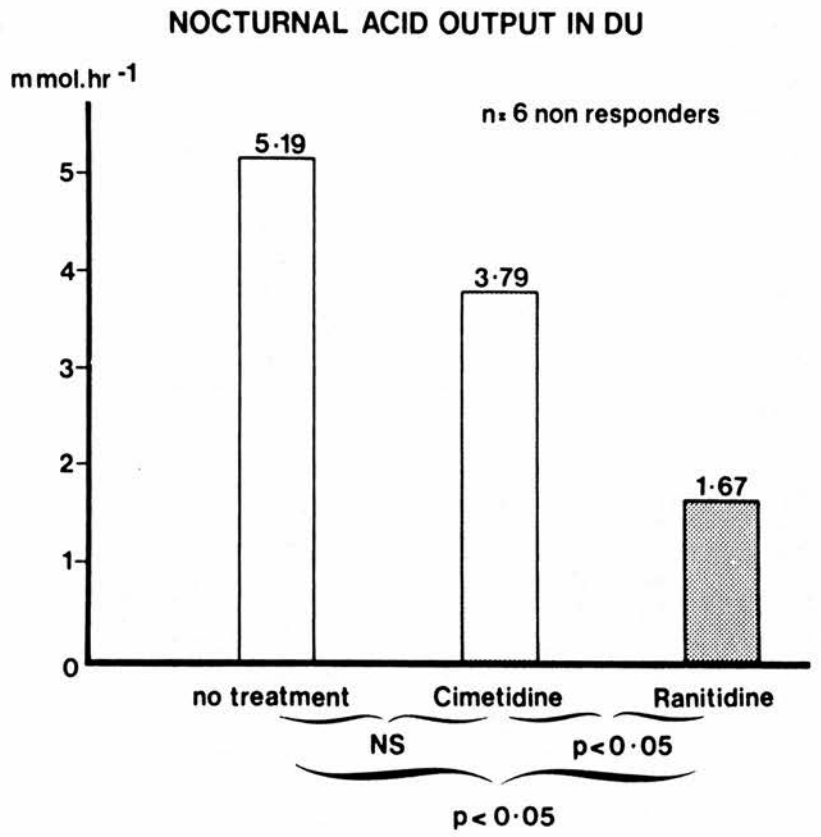
Mean Nocturnal Hydrogen Ion Activity

Figure 6.2.1



Mean Nocturnal Volume of Secretion

Figure 6.2.2.



Mean Nocturnal Acid Output

Figure 6.2.3.

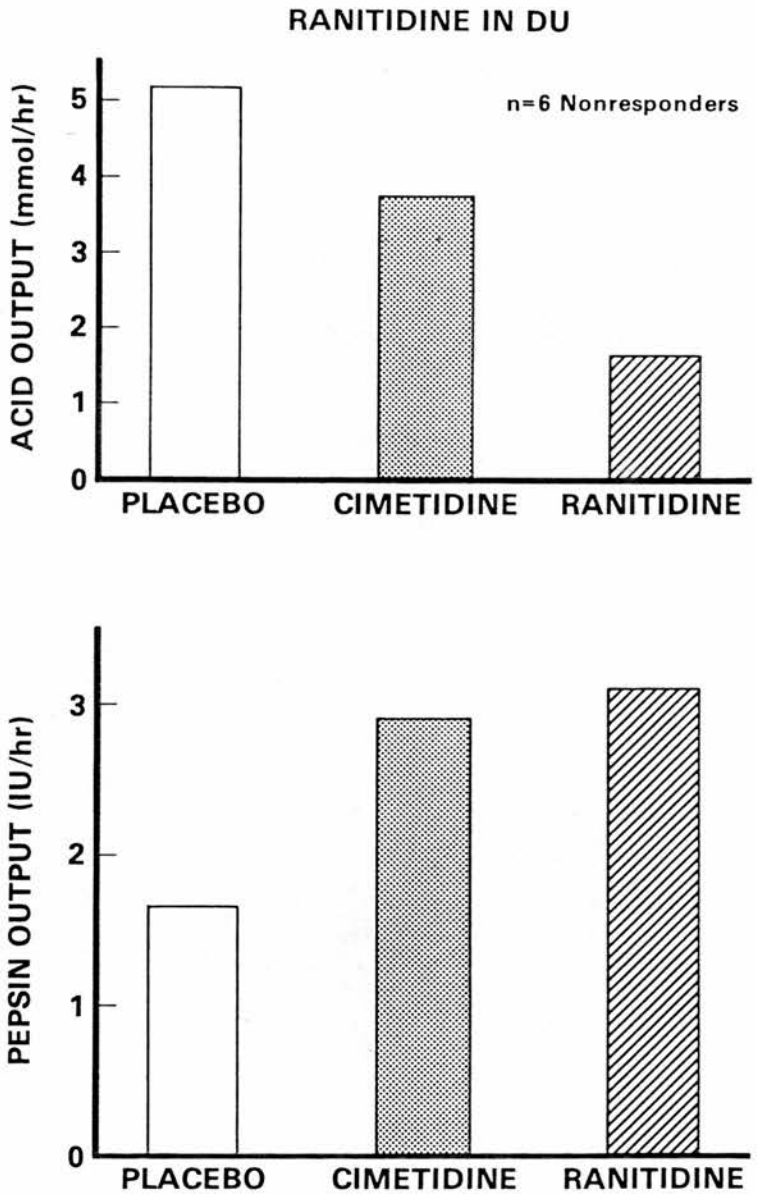


Figure 6.2.4

Mean nocturnal acid and pepsin output.

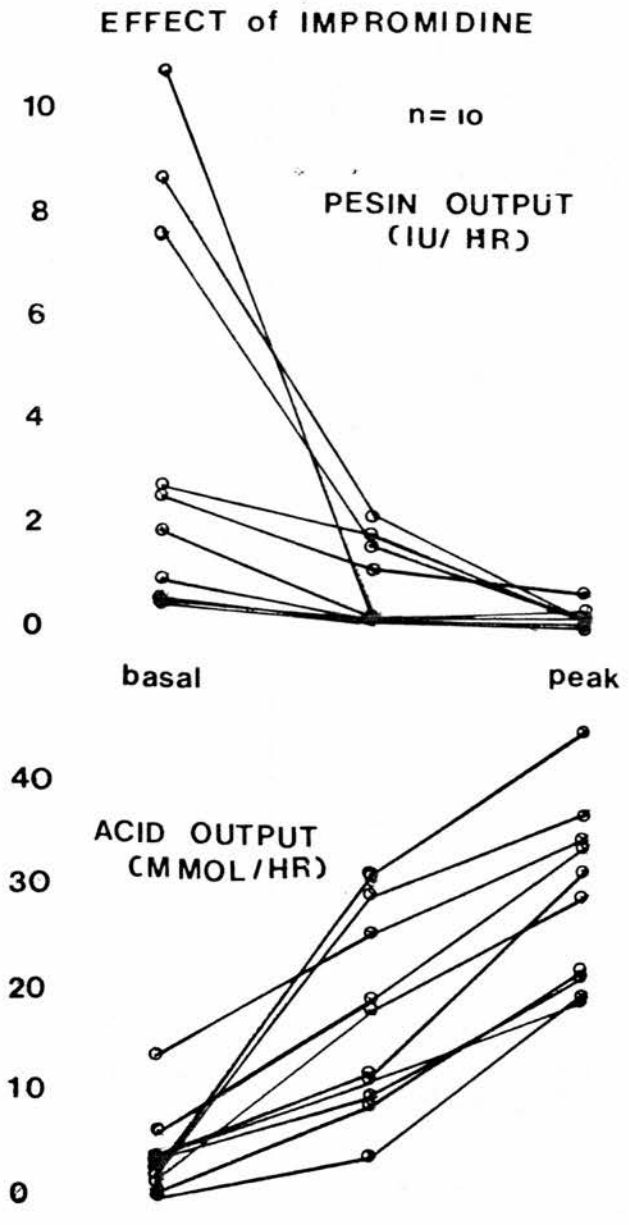


Figure 6.3.1

Acid and pepsin outputs in response to impromidine.

These results suggest that H_2 agonism increases acid output but decreases pepsin output in normal subjects.

6.4. Glucose and Insulin. Sufficient serum had been stored from study 2.3.2 to measure glucose levels on the two treatments in six patients and insulin levels on the two treatments in four patients.

The results are shown in Figures 6.4.1 and 6.4.2. It can be seen that there was no difference between hourly glucose or insulin levels on no treatment and cimetidine.

6.5. Cimetidine combined with atropine 4.8mg/day. Mean nocturnal hydrogen ion activity (Figure 6.5.1) decreased by 39% with cimetidine 1g/day (NS), by 19% with atropine 4.8mg/day (NS) and by 69% with the combination of cimetidine 1g/day and atropine 4.8mg/day ($p<0.05$ compared with placebo NS compared to cimetidine 1g/day and $p< 0.001$ compared with atropine alone). This result was not statistically different from cimetidine 1g/day because one patient had a remarkably good response to cimetidine alone which was slightly better than the combination.

Mean 24 hour hydrogen ion activity (Figure 6.5.2) decreased by 35% with cimetidine (NS) by 28% with atropine (NS) and by 73% with the combination ($p< 0.01$ compared with no treatment, $p< 0.001$ compared with cimetidine and $p < 0.001$ compared with atropine).

Volume of gastric secretion is shown in Figure 6.5.3. It can be seen that volume again did not decrease significantly in the nonresponders on cimetidine, but there was a highly significant reduction from 80.5ml/hr on placebo to 16.5ml/hr with the combination ($p< 0.01$). It can also be seen that atropine alone decreased volume when compared to placebo ($p< 0.02$) but this decrease was not as great as the combination.

Acid output (Figure 6.5.4) decreased by 83% with the combination ($p< 0.01$ compared with no treatment, $p< 0.01$ compared with cimetidine

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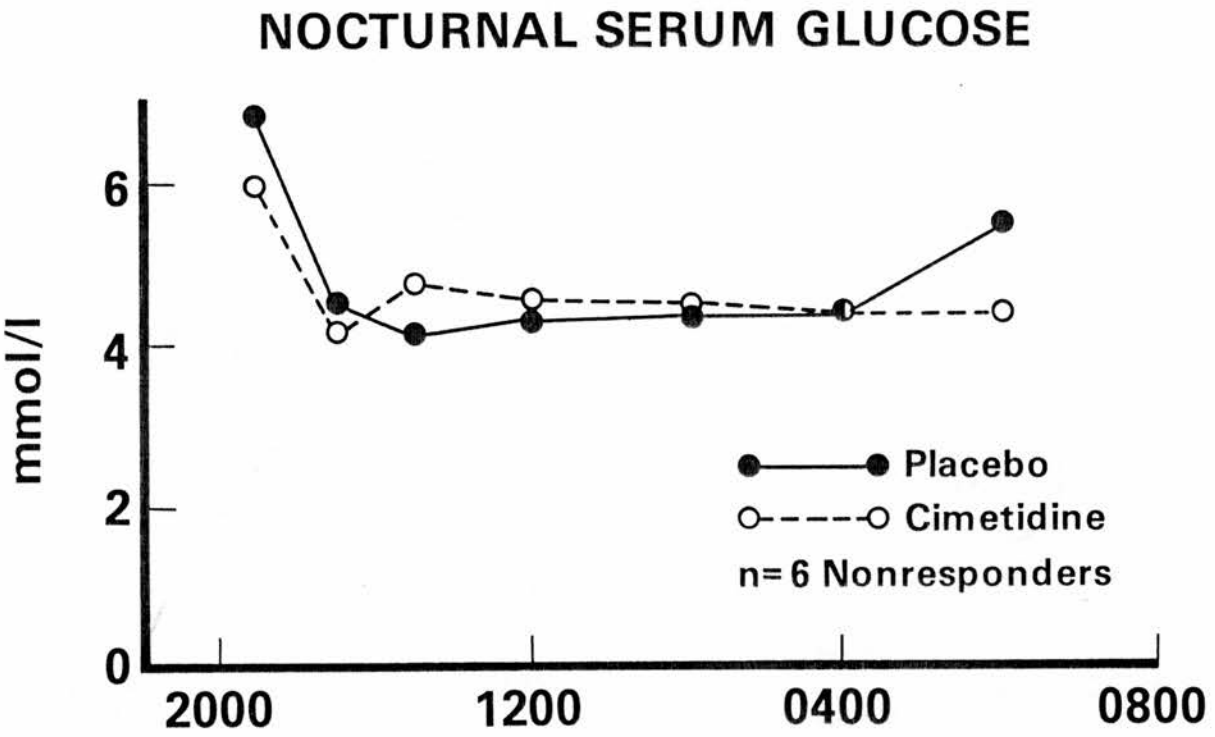


Figure 6.4.1.

The effect of cimetidine on nocturnal serum glucose.

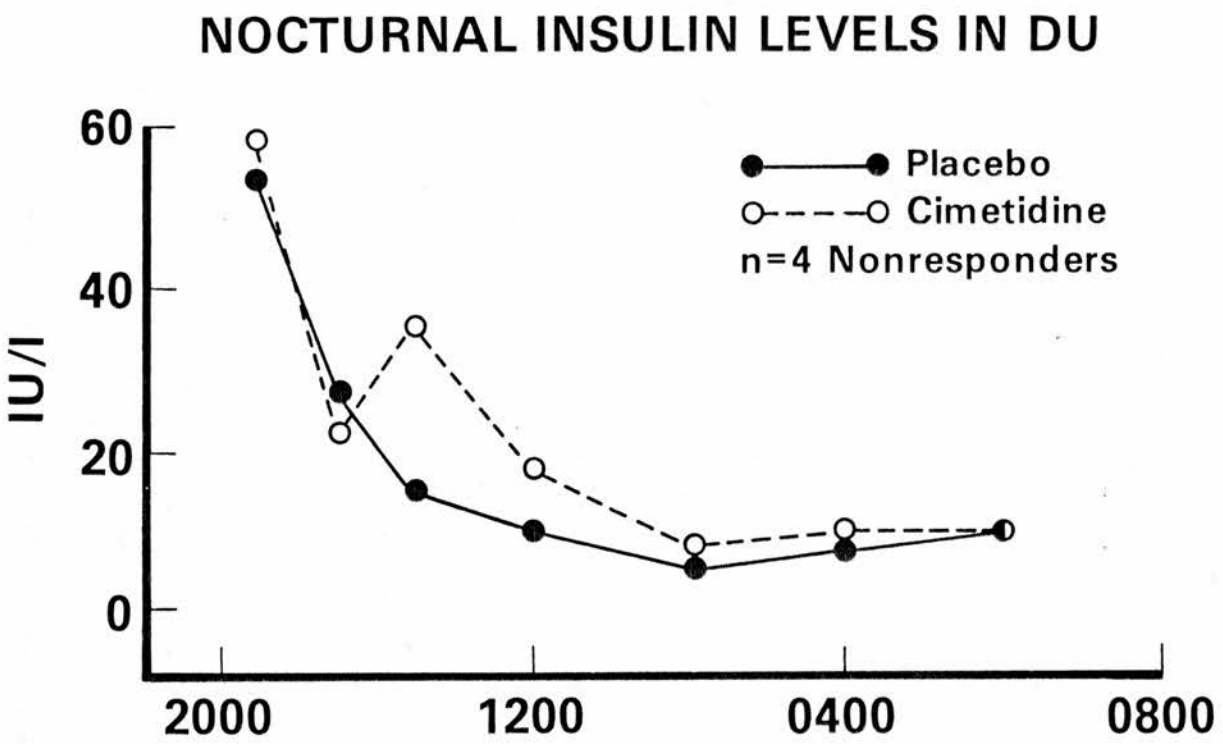
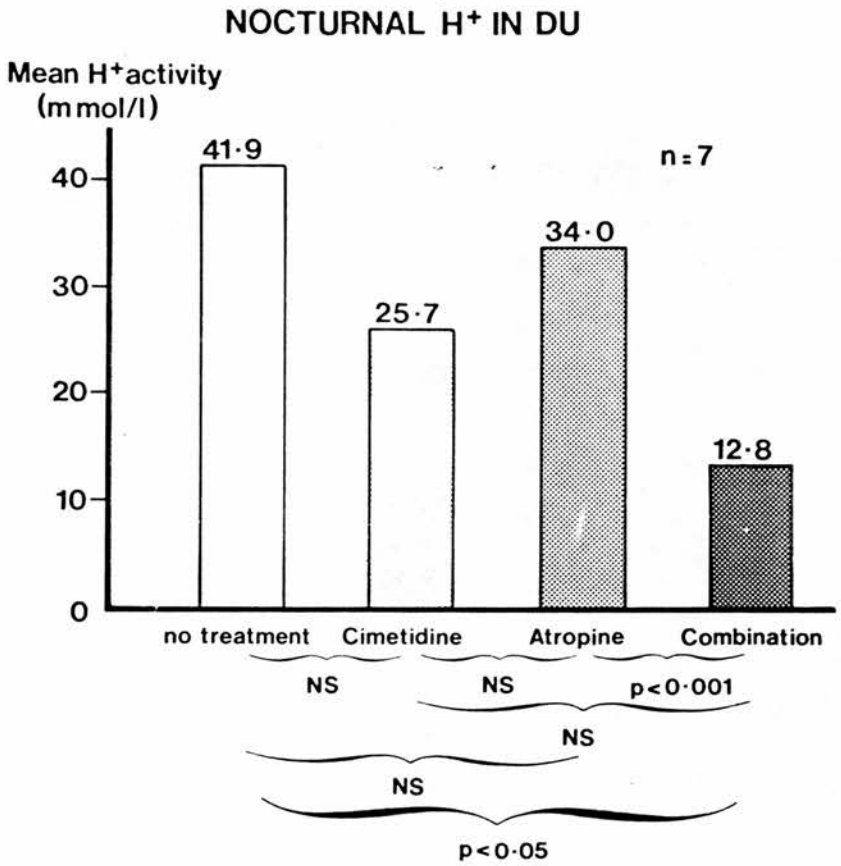


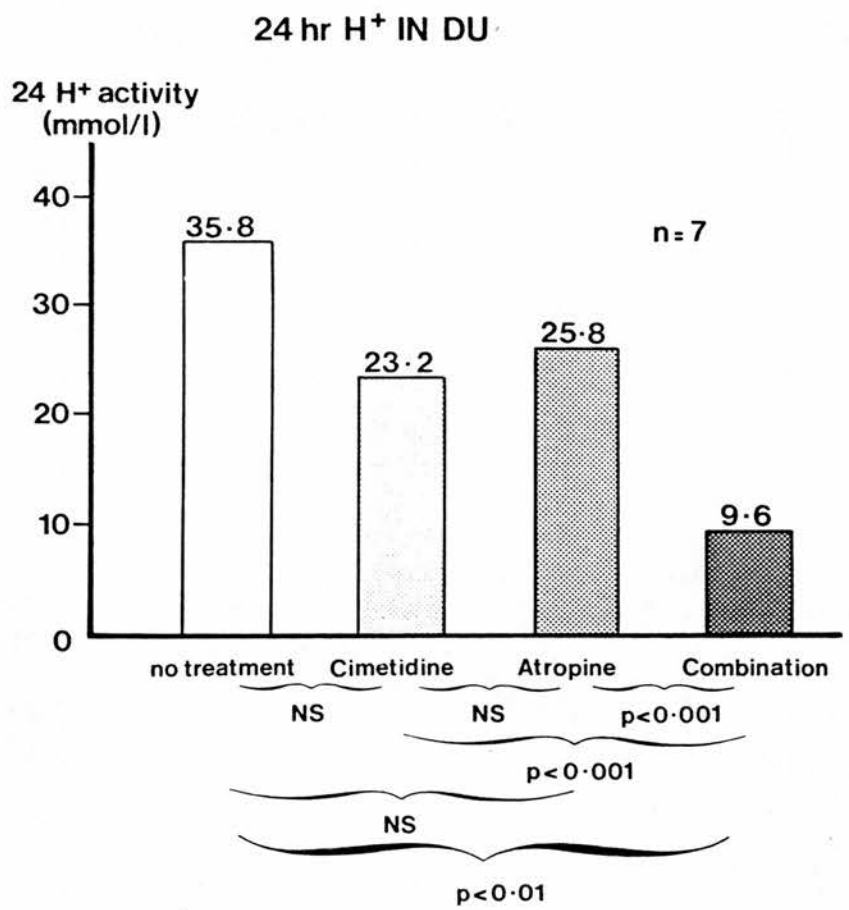
Figure 6.4.2.

The effect of cimetidine on nocturnal serum insulin.



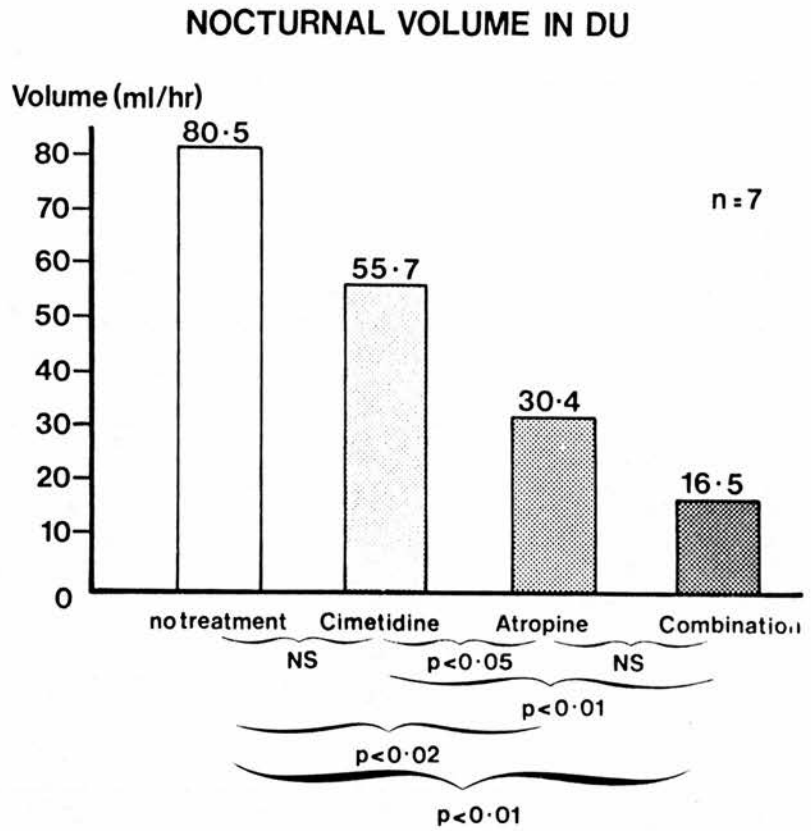
Mean nocturnal hydrogen ion activity

Figure 6.5.1.



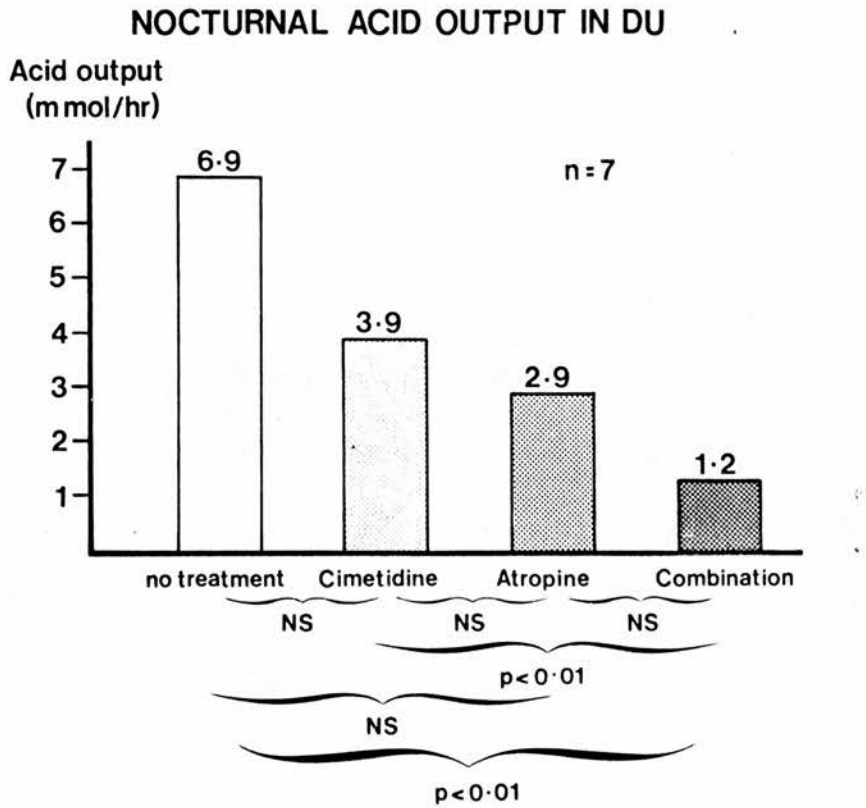
Mean twentyfour hour hydrogen ion activity

Figure 6.5.2



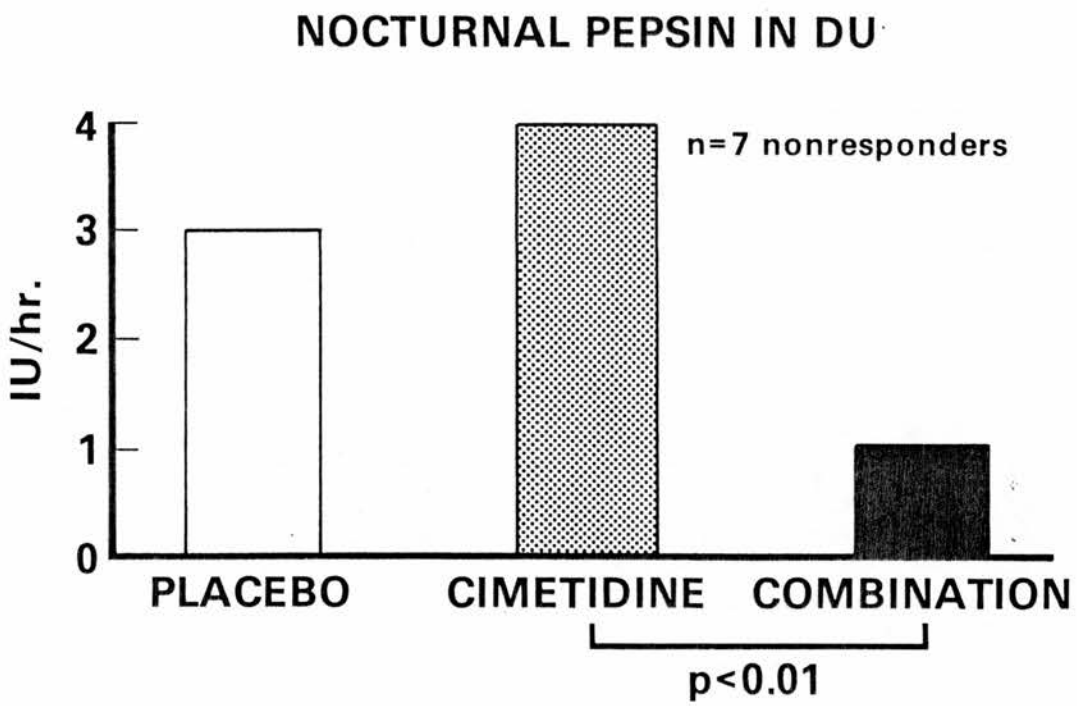
Mean Nocturnal Volume of Secretion

Figure 6.5.3



Mean Nocturnal Acid Output

Figure 6.5.4



Mean Nocturnal Pepsin Output

Figure 6.5.5

and NS compared with atropine alone).

Mean nocturnal pepsin output (Figure 6.5.5) was 3.03 ± 3.91 IU/hr on no treatment, 4.0 ± 3.2 IU/hr on cimetidine alone and 1.1 ± 1.13 IU/hr on the combination ($p < 0.01$ compared with cimetidine alone).

The result shows that combination of atropine 4.8mg/day with cimetidine 1g/day is superior to either drug alone at decreasing 24 hour intragastric acidity, nocturnal intragastric acidity, nocturnal volume of secretion, acid output and nocturnal pepsin output.

CHAPTER 7

DISCUSSION

7.1 Nocturnal Pepsin Secretion. The method of measuring pepsin concentration used in this thesis had an extremely good correlation with another more standard method (Berstad 1970) but had the advantage of being quicker and providing a large throughput. Taylor (1970) has shown that pepsin may be separated into several proteolyte enzymes. However, although some of these enzymes are closely associated with duodenal ulcer, it is probably total proteolytic activity which keeps an ulcer active because total peptic activity is related to ulcer activity (Taylor 1970; Elder 1975; Venables 1979; Achord 1978; Helmer 1937; Achord 1981).

The study confirms the results of the previous experiments by showing less decrease in acid output in the nonresponders compared with other duodenal ulcer patients. The findings also suggest that nocturnal intragastric pepsin is increased by cimetidine in duodenal ulcer patients. The highest nocturnal pepsin levels were found in the nonresponders receiving cimetidine.

Animal work suggests that duodenal ulcer does not occur in the absence of pepsin (Schiffrin and Warren 1942) and in man, pepsin secretion has been correlated with disease activity (Vanzant, Osterberg, Alverez, Rivers 1933; Taylor 1970; Elder 1975; Venables 1979; Achord 1978; Helmer 1937). Increased pepsin secretion is unlikely to be of clinical benefit and may be an important cause of nonresponse.

Cimetidine has been shown to increase ulcer healing rates (Bodemar and Walan 1976; Gray, McKenzie, Smith, Crean, Gillespie 1977; Domschke, Domschke, Lux, Demling 1976) and previous reports suggest that cimetidine either has no effect or decreases nocturnal pepsin secretion (Longstreth, Malagdelada, Go 1975; Longstreth, Go, Malagdelada 1976; Saunders, Cargill, Wormsley 1977). These reports contradict the findings of this study.

Pepsin is irreversibly denatured above pH 6.0 (Figure 7.1.1)

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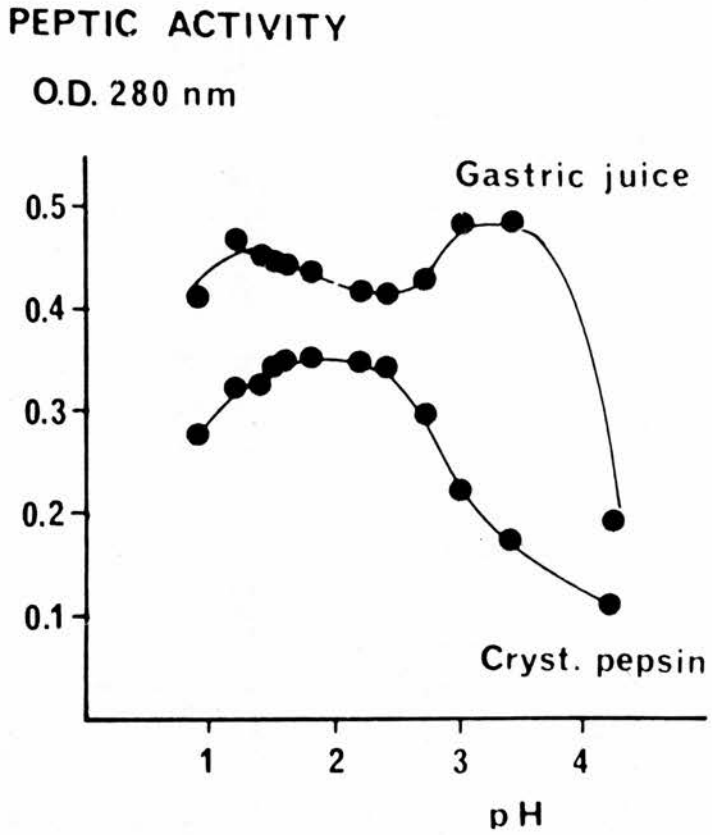

The pH Stability Curve of Pepsin (Berstad 1982)

Figure 7.1.1

(Goulding, Borsook, Wasteneys 1927; Piper and Fenton 1973; Berstad 1982). If any treatment results in a rise in pH, pepsin deactivation will result, providing a falsely low pepsin measurement. In nonresponders, it has already been demonstrated that cimetidine has a decreased effect on hydrogen ion activity and, therefore, pepsin is unlikely to be denatured. Previous reports measuring the effect of cimetidine on pepsin secretion were all performed in either normal subjects or duodenal ulcer patients who had a much greater decrease of hydrogen ion activity than any of the present studies.

The increase of pepsin output observed in this study occurred in both nonresponders and other duodenal ulcer patients. The question which arises is "does this increase occur as part of the pathophysiology of duodenal ulcer, or part of a physiological pathway in normal subjects"?

Duodenal ulcer is thought to be associated with increased vagal drive (Dragstedt 1945) and there have been several unexplained reports suggesting a combination of vagal stimulation with an H_2-receptor antagonist results in a greater intragastric pepsin concentration than produced by vagal stimulation alone (Carter, Forrest, Logan, Ansell, Lidgard, Heading and Shearman 1976; Sheers and Roberts 1981; Gibson, Hirschowitz and Hutchison 1974). Thus H_2 blockade might only increase pepsin output in the presence of increased vagal tone.

Several other workers have noted increased pepsin output with cimetidine. Browning and Heathcote (1982) found an increase in pepsin concentration in the cat after cimetidine; Stage, Stadil and Fischerman (1978) demonstrated a significant increase in basal pepsin output in nine patients with Zollinger-Ellison syndrome receiving cimetidine and Pikkarainen (1981) found an elevated serum pepsinogen after cimetidine treatment in duodenal ulcer patients.

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Before investigating normal subjects, it was decided to see if other H_2 antagonists resulted in increased pepsin secretion or whether this is an effect peculiar to cimetidine. The next study, therefore, measured nocturnal pepsin secretion in duodenal ulcer patients receiving ranitidine.

7.2 Ranitidine. Ranitidine is a new furan histamine H_2-receptor antagonist which inhibits all forms of stimulated acid secretion (Muller-Lissner, Sonnenberg, Eichenberger, Blum 1981; Sheers and Roberts 1981) and has been shown to provide a 70% inhibition of mean 24 hour intragastric acidity and a 90% reduction of nocturnal acid output (Walt, Male, Hunt, Rawlings, Milton-Thompson and Misiewicz 1981).

The aim of this study was to compare the effect of this new, more potent H_2-receptor antagonist with cimetidine at decreasing 24 hour intragastric acidity, volume of nocturnal secretion and acid output in nonresponders and to investigate the effect of ranitidine on nocturnal pepsin secretion.

The study demonstrated that ranitidine was more effective at reducing 24 hour intragastric acidity, nocturnal intragastric acidity, and nocturnal acid output than cimetidine. Like cimetidine in the previous studies, ranitidine had no significant effect on volume of gastric secretion. This may have been because the number of patients was small. However, acid output and intragastric acidity did not decrease significantly. Work with ranitidine in dogs (Brittain and Daly 1981) has shown that only after a very large reduction in volume (78-80%) is concentration of acid reduced - and then by only about 20%. Thus, whatever mechanism is involved in nonresponse to cimetidine, it is likely that the same mechanism exists for ranitidine. This is also supported by the present observed reduction of 63% in intragastric acidity and 70% in nocturnal acid output compared to

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70% and 90% respectively reported by Walt, Male, Hunt, Rawlings, Milton-Thompson and Misiewicz (1981) in unselected duodenal ulcer patients.

There have been three previous reports of ranitidine healing cimetidine resistant ulcers (Mohammed, Mitchell, McKay 1981; Brunner 1981; Schultz 1982), but these were not controlled studies and it is known that continued treatment with cimetidine results in increased healing rates (Bardhan 1980). A recent report suggested that although ranitidine heals cimetidine resistant ulcers, cimetidine can also heal ranitidine resistant ulcers (Mazzacca, D'Agostini, D'Arienzo, Piai, Sabbatini and Verre 1982).

Clinical trials comparing rantidine with cimetidine have tended to show slightly higher healing rates with ranitidine but none of these have been significant (Langman, Henry, Ogilvie 1981; Walt, Trotman, Frost, et al 1981; Costello, Fielding and Lee 1982). However, to demonstrate less than a 10% difference in healing rates between two different treatments requires extremely large numbers of patients.

The present study suggests that ranitidine increases nocturnal pepsin output to a greater extent than cimetidine. The number of patients was small and the standard deviations quite large and, therefore, the difference was not significant. However, it is in direct contrast to the acid results and, therefore, must be suggestive.

Müller-Lissner, Sonnenberg, Eichenberger and Blum (1981) have shown that sham feeding stimulated pepsin output decreased with ranitidine, but they also showed over a hundredfold decrease in acid concentration which would have resulted in pepsin deactivation. Sheers and Roberts (1981) found pepsin concentration increased when ranitidine was added to a vagal stimulus; Cavallini, Angelini, Fratton, Ruta, Rosa, Delorio and Scuro (1982) found an increased pepsin in gastric juice after ranitidine treatment and Mario, Plebani, Vionello, Forini,

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Giordano, Scalabrin, Cerotti and Naccerato (1980) found increased serum pepsinogen after ranitidine treatment in duodenal ulcer patients.

It thus appears that H_2 blockade results in increased intragastric pepsin secretion in duodenal subjects. Normal subjects do not show this effect because either it is part of the pathophysiology of this disease or the associated greater increase in pH with H_2 blockade in healthy individuals results in pepsin deactivation.

If H_2 blockade results in a rise of intragastric pepsin then H_2 agonism should produce a fall. As H_2 agonism is accompanied by an increased acid secretion, autodestruction of pepsin will not be a problem, even in normal subjects. Impromidine, a recently described selective H_2 agonist (Hunt, Mills, Beresford, Billings, Burland and Milton-Thompson 1980) was, therefore, used to measure basal and stimulated pepsin output in a group of healthy volunteers.

7.3 Impromidine in normal subjects. The aim of this study was to measure the effect of impromidine on pepsin secretion in normal subjects. The result shows a significant decrease in pepsin output after impromidine and a significant increase in acid secretion. This suggests there is a physiological pathway in man by which histamine inhibits pepsin secretion. The findings do not support a pathophysiological mechanism of pepsin secretion associated with duodenal ulcer alone.

There have been no previous reports of pepsin secretion with impromidine but several authors have described pepsin output in response to histamine. Babkin (1930) found pepsin output decreased with histamine, but he thought this might be a "washout" phenomenon. The present study does not support this concept because pepsin output decreased even in the first half hour of impromidine infusion.

Alley was the first to suggest that histamine had an inhibitory

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effect on the peptic cell. In 1935, he wrote "histamine, while stimulating the parietal cells, inhibits that action of the vagi on the peptic cells preventing the discharge by them of zymogen granules". Hirschowitz has also suggested that histamine inhibited pepsin output (Hirschowitz 1957) in the dog and later demonstrated a dose response effect (Hirschowitz, Sachs and Hutchison 1974). Emas and Grossman (1967) have shown that in the dog, histamine in large doses inhibits pepsin secretion and more recently Gibson, Hirschowitz and Hutchison (1974) suggested that histamine may have an inhibitory role on the peptic cell in man.

Pepsin is released by chief cells which may be stimulated either locally, hormonally, or neuronally. Johnson (1972a; 1972b) has shown that local application of acid results in increased pepsin release. However, although Hirschowitz and Gibson (1973) and Guldvag and Berstad (1982a) have postulated a direct inhibitory action of histamine on the chief cell, studies on isolated canine and rabbit cells (Sol, Amirian, Thomas, Ayalon 1982; Kapadia, Donaldson 1976; Kasbekar, Jensen and Gardner 1982) have shown neither stimulation nor inhibition of pepsin output in response to histamine.

Secretin is known to stimulate pepsin release (Sol, Amirian, Thomas, Aylon 1982; Raufman, Kasbekar, Jensen and Gardner 1982; Berstad, and Peterson 1970; Berstad, Peterson, Roland and Liavig 1973; Brooks, Isenberg and Grossman 1979) but this hormone does not increase with ranitidine after tetragastrin (Yabana, Kawai et al 1982) or with ranitidine after either a fast or a meal (Tomassetti, Pazzaglia, Stanghellini, Bonora, Favaro, Vezzadini and Labo 1982).

Cimetidine is known to increase serum gastrin (Spence, McCormick, Oliver and Celestin 1978; Forrest, Fettes, McLoughlin and Heading 1978;

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Richardson 1978) and might be involved in controlling pepsin secretion. Schofield (1958) demonstrated that food decreased pepsin output in the dog Heidenhein pouch which led him to conclude inhibition may occur via a hormonal pathway. In the antrectomised dog model, Olbe, Ridley and Uvnas (1968) demonstrated both gastrin and histamine decreased vagally stimulated pepsin secretion and more recently Magee and Hu (1975) have suggested gastrin may have an inhibitory effect on pepsin release. The same group (Kondo and Magee 1977) later demonstrated that the antrum is the source of an agent which inhibits pepsin secretion but they favoured a mechanism involving sympathetic nerves rather than gastrin. Thus, although cimetidine increases gastrin release, it does not explain an associated increase in pepsin as gastrin, if anything, decreases pepsin secretion. However, cimetidine is known to have a number of other hormonal effects (Edwards 1981), any of which might be responsible for raising intragastric pepsin.

Pepsin is also released as a result of cholinergic stimulation (Venables, Wheldon and Johnston 1975; Venables and Johnston 1969; Wilson, Dymock and Cowley 1974; Berstad, Peterson, Roland Liavig 1973) and if histamine has an inhibitory role on the vagus nerve then cimetidine should decrease vagal inhibition resulting in increased pepsin output. Maybury and Carr-Locke have shown that cimetidine had no effect on insulin stimulated secretion in cimetidine nonresponders which supports H_2 blockade increasing vagal drive. The lack of effect on volume of secretion shown throughout this thesis, the increased pepsin secretion with cimetidine and ranitidine and the close correlation of acid and pepsin output with cimetidine also support this theory. The latter observation demonstrated in study 6 suggests that when on cimetidine, acid and pepsin are under the same control which might well be vagal in origin.

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Vagotomy results in decreased histamine stimulated acid secretion (Payne and Kay 1962; Rosato, Rosato, and McFadyen 1971) and does not support histamine having an inhibit-ory action on the vagus unless there are two types of nerve fibre, one affecting chief cells and one affecting parietal cells. Ingolby, Man and Spencer (1982) have shown that although sham feeding results in increased intragastric histamine, insulin stimulated secretion does not, suggesting the presence of two types of vagal fibre.

Insulin induced hypoglycaemia increases vagal drive with resulting increased pepsin output. If cimetidine stimulated insulin release, this could well explain the previous results. It was, therefore, decided to measure nocturnal serum insulin and glucose in response to cimetidine.

7.5 Glucose and Insulin. The result demonstrated that cimetidine had no significant effect on serum insulin or serum glucose in cimetidine nonresponders and, therefore, does not support the suggestion that increased vagal drive results from nocturnal hypoglycaemia.

Two possibilities remain; either cimetidine causes release of a hormone resulting in increased pepsin output or cimetidine increases vagal drive in some types of vagal fibre which are normally inhibited by histamine. The latter possibility could be explained by a decreased synthesis or release of enkephalins which are known to inhibit acid and pepsin secretion (Sullivan, Corke and Darwish 1982; Konturek, Kwiecien, Obtulowicz, Swierczek, Oleskyend and Coy 1982) and are found in large quantities in the gastric antrum (Edin, Lundberg, Terenius 1980; Polak, Sullivan, Bloom, Facer and Pearce 1977) and vagus nerve (Alumets, Hakanson, Sundler and Chang 1978). However, both cimetidine and enkephalin analogues result in increased serum prolactin secretion (Knigge, Wollesen, Dejgarrd, Thuesen, and Christiansen 1981;

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vonGraffenried, delPozo, Roubieck, Krebs, Poldinger, Burmeister and Kerp 1978; Stubbs, Delitala, Jones, Jeffcoate, Edwards, Ralter, Besser, Bloom and Alberti 1978) and, therefore cimetidine would, if anything be expected to increase enkephalin release.

The aim of this thesis set out to ask why patients do not respond to H_2 blockade and how these nonresponders should be treated. It did not include investigating the mechanism involved in nonresponse and, therefore, other studies, perhaps measuring overnight hormone or enkephalin release were not performed. One final question, however, is to ask how the nonresponder should be treated. The previous discussion has suggested that increased vagal drive may result with cimetidine treatment. To inhibit this response, the logical approach would be to add an anticholinergic agent to cimetidine yet the result of study 3.3 and that reported by Pounder, Hunt, Vincent, Milton-Thompson and Misiewicz (1977) showed no benefit from combination therapy. Previous reports, however, (Thjodleifsson and Wormsley 1974; Londong, Londong, Weber and VonWerder 1980) did find benefit from the addition of an anticholinergic agent. The study in 3.3 and that previously reported by Pounder and colleagues were performed at the Royal Naval Hospital, Haslar, using fit naval ratings whose mean weight in the present study, for example, was 73.3 kg. Few of these subjects complained of side effects from the atropine and, therefore, the dose on a body weight basis may have been insufficient. It was, therefore, decided to repeat the study combining cimetidine with atropine but to increase the dose to the maximum considered safe by the British Pharmacopea of 4.8mg/day.

7.5 Cimetidine combined with atropine 4.8mg/day. The aim of this study was to measure the effect of cimetidine 1g/day combined with atropine 4.8mg/day on 24 hour intragastric acidity, nocturnal volume

of gastric secretion, nocturnal acid output and pepsin output in non-responders. The result is in agreement with previous experiments suggesting cimetidine alone has no significant effect on the volume of nocturnal gastric secretion. The addition of atropine at the increased dose produced a dramatic decrease in 24 hour hydrogen ion activity, nocturnal hydrogen ion acitivity, nocturnal volume of secretion and nocturnal acid output. Cimetidine alone produced an increase in nocturnal pepsin output which was abolished by the addition of atropine.

These results suggest that insufficient dose of atropine was the probably explanation for the lack of benefit of atropine 2.4mg/day in 3.3 and in the study reported by Pounder, Hunt, Vincent, Milton-Thompson and Misiewicz (1977). The present study also suggests that whatever mechanisms involved in failure to respond to cimetidine, it is abolished by adding an anticholinergic agent.

The decrease in peptic activity with the addition of atropine supports the theory of increased vagal drive by cimetidine. The result could, however, also be explained by the combination producing a greater increase in pH than with cimetidine alone and, therefore, increased pepsin deactivation.

Whatever mechanism is involved, adding an anticholinergic agent should result in increased healing rates. Atropine however has notable side effects in the present study, and all patients complained that these were unacceptable.

Pirenzepine is a new antimuscarinic agent with a high affinity for receptors at the parietal cell and, therefore, is without systemic side effects (Jaup 1981).

Gabryelewicz, Serosick, Laszewicz and Piotrowski (1982) have shown ranitidine combined with pirenzepine inhibits pentagastrin stimulated acid secretion better than ranitidine alone and Londong, Londong,

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Weber and VonWerder (1980) have shown that pirenzepine combined with cimetidine inhibits pentagastrin stimulated acid secretion better than either drug alone. Mignon, Vallot, Galmiche, Dupas and Bonfils (1980) have used this latter combination with some success in the Zollinger-Ellison syndrome. Nocturnal acid output has been inhibited better with a combination of an H_2-receptor antagonist with pirenzepine than an H_2-antagonist alone, and has been recommended as a form of therapy for the resistant ulcer (Scholton, Schuchert, Fritsch, Muller and Hengels 1982). Roberto, Nicola and Sergio (1982) gave a combination of cimetidine and pirenzepine to 15 patients who failed to respond with cimetidine or pirenzepine both given separately for one month. Thirteen of the 15 patients healed their ulcer within one month of taking the combination therapy. Although this was not a controlled study, it supports the work in this thesis that cimetidine nonresponders should be treated with a combination of cimetidine and an anticholinergic agent.

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CHAPTER 8

CONCLUSION

8. Conclusion. It has been demonstrated that in nonresponders, cimetidine has no significant effect on volume of gastric secretion and a decreased effect on intragastric pH and nocturnal acid output when compared with a unselected group of duodenal ulcer patients. The drug may also cause increased release of pepsin in these patients. It is suggested that the combination of these factors results in failure to heal or early relapse. The mechanism of increased pepsin output with cimetidine was thought to be an H_2 effect because ranitidine resulted in increased intragastric pepsin, and the H_2 agonist impromidine inhibited pepsin release.

Increasing the dose of cimetidine does not improve control of acid secretion despite adequate drug absorption. Combination of cimetidine with an anticholinergic agent however, results in a dramatic decrease of both acidity and pepsin secretion.

It is, therefore, probable that addition of an anticholinergic agent to cimetidine will result in healing of a cimetidine resistant ulcer. If, however, surgery is indicated, good results are to be expected from proximal gastric vagotomy as this gives better control of acidity and acid output than cimetidine alone.

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ACKNOWLEDGEMENTS

I am sincerely grateful to Dr. R.H. Hunt for advice and suggestions. He started the work on the nonresponders and sparked off my enthusiasm.

I thank Angela Pual, Jan McEwan and Maxine Buck for help in collecting gastric secretion and, particularly Maxine Buck who found and organised patients and volunteers.

The work would not have been possible without the generous support of Smith, Kline and French who financed my year at Haslar and supported most of the studies. They also arranged for serum cimetidine estimations.

I thank Dr. D.G. Colin-Jones for allowing me to study his patients and for his encouragement throughout the year. I extend my thanks to the Royal Navy for providing facilities at Haslar, and particularly to the Department of Graphics and Medical Photography for providing the illustrations. I am also grateful to Mr. Stephen Gray and Mr. John Billings for measuring all the pepsin levels and, the Department of Nuclear Medicine, Haslar Hospital for serum gastrin estimations.

I thank Mr. Chris Venables, Department of Surgery and Dr. David Saunders, Department of Physiology, Newcastle Medical School for measuring serum insulin and glucose levels.

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BIBLIOGRAPHY

1. Achord, J.L. (1978)

Comparison of basal gastric acid and pepsin output in controls vs active duodenal ulcer disease.

Am.J.Gastroenterol. 70:46-49

2. Achord, J.L. (1981)

Gastric pepsin and acid secretion in patients with acute and healed duodenal ulcer.

Gastroenterology 81:15-18

3. Alley, A. (1935)

The inhibitory effect of histamine on gastric secretion.

Am.J.Dig.Dis. and Nutrition 1:787

4. Alumets, J. Hakanson, R. Sundler, F. and Chang, K.J. (1978)

Leu-enkephalin like material in nerves and enterochromaffin cells of the gut.

Histochemistry 56:187-196

5. Amdrup, E. and Johnston, D. (1970)

110 highly selective vagotomies without drainage (HSV) for duodenal ulcer.

Gut 11:1062

6. Amdrup, E. and Jensen, H.E. (1970)

Selective vagotomy of the parietal cell mass preserving innervation of the undrained antrum.

Gastroenterology 59:522-527

7. Anderson, W. and Watt, J. (1959)

Inhibition of peptic activity protection against histamine ulceration in the guinea pig and combination with gastric mucin by an algal polyanion.

J.Pharm.Pharmacol. 11:318

...105

8. Anson, M.L. and Mirsky, A.E. (1932)
The estimation of pepsin with haemoglobin.
J.Gen.Physiol. 16:59-63

9. Ash, A.S.F., and Schild, H.O. (1966)
Receptors mediating some actions of histamine.
Br.J.Pharmac.Chemother. 27:427-429

10. Ashford, C.A., Heller, H. and Smart, C.A. (1949)
The effect of antihistamine substances on gastric secretion in man.
Br.J.Pharmac. 4:157-161

11. Babb, R.R. (1981)
Drug interactions with cimetidine.
Postgrad.Med. 70:60-64

12. Babkin, B.P. (1930)
The value of histamine as a test of gastric secretion from a physiological point of view.
Can.Med.Assn.J. 23:268-272

13. Babkin, B.P. and Komorov, S.A. (1932)
The influence of gastric mucus on peptic digestion.
Can.Med.Assn.J. 27-463-469

14. Babkin, B.P. (1938)
The abnormal functioning of the gastric secretory mechanism as a possible factor in the pathogenesis of peptic ulcer.
Can.Med.Assn.J. 38-421-429

15. Balroni, H.M.M., Ross, I.N. and Turnberg, L.A. (1981)
The 'mucus bicarbonate barrier' demonstration of a pH gradient within the mucus layers of the stomach.
Br.J.Surg. 68:365

16. Barbezat, G.O., and Bank,S. (1976)
Effect of a histamine H_2-receptor antagonist and an anticholinergic on gastric acid secretion in man.
S.Afr.Med.J. 50:849

...106

17. Bardhan, K.D. (1980)
Intermittent treatment of duodenal ulcer with cimetidine.
Br,.Med.J. 11:20-22

18. Bardhan, K.D. (1981a)
The economic consequences. In: Perspectives in Duodenal Ulcer. (ed. Bardhan, K.D. 1981), Smith, Kline & French Laboratories Ltd. Welwyn, Garden City, Herts,P14.

19. Bardhan, K.D. (1981b)
What happens to duodenal ulcers that do not respond quickly to cimetidine?
Gut 1981 :22:A880

20. Bardhan, K.D. (1981c)
Nonresponders to cimetidine. In:Cimetidine in the 80's. (ed. Baron, J.H.) Churchill Livingstone 1981 :42-57

21. Bardhan, K.D. and Hinchliffe, R.F.C. (1981)
Effect of cimetidine on surgery for duodenal ulcer.
Lancet 2:38

22. Barger G., and Dale, H.H. (1911)
B imidazolylethylamine, a depressor constituent of intestinal mucosa.
J.Physiol.Lond. 41:499-503

23. Barnard, J., Darkin, D.W., Viney, N.J., Ahmet, Z., Lightfoot, N.F., Hunt, R.H., and Milton-Thompson G.J. (1981)
Effect of cimetidine on twenty-four hour intragastric pH, bacterial flora and concentrations of nitrite and nitrosocompounds.
Gut 22:A873

24. Baron, J.H. (1963)
No acid no ulcer
Lancet 1:385-386

...107

25. Baron, J.H. (1972)

Aetiology. In: Chronic Duodenal Ulcer. (ed.Wastell,C). Butterworths London; p19-52

26. Baron, J.H. (1973)

The clinical application of gastric secretion measurements. Clinics in Gastroenterology 2:293-314

27. Beaumont, W. (1833)

Experiments and observations on the gastric juice and physiology of digestion. Plattsburg, F.G. Allen.

28. Bennet, J.H., McCormick, D.A., Oliver, J.M., and Celestin, L.R. (1978)

The treatment of oesophagitis and gastro-oesophageal reflux disease with cimetidine. In:'Cimetidine The Westminster Hospital Symposium' (ed. Wastell, C. and Lance, P.) Churchill-Livingstone, Edinburgh. p147-152.

29. Berstad, A. (1970)

A modified haemoglobin substrate method for the estimation of pepsin in gastric juice.

Scand.J.Gastroenterol. 5:343-348

30. Berstad, A. and Peterson, H. (1970)

Effect of secretin on histamine and pentagastrin secretion of pepsin in man.

Scand.J.Gastroenterol. 5:59-63

31. Berstad, A., Peterson, H., Roland, M., and Liavag, I. (1973)

Effect of secretin on pentagastrin stimulated gastric acid and pepsin secretion after vagotomy in man.

Scand.J.Gastroenterol. 8:119-122

32. Berstad, A. (1982)

Do antacids inhibit pepsin? In:'Antacids in the Eighties' (ed. Halter, F.)Urban dn Schwarzberg, Munchen-Wien-Baltimore. Chapt.3: 17-22

....108

33. Bernarde, C. (1856)
Lecons de physiologigice experimentale applique a l medecine.
Vol.II, Chapter 16:406-418. Paris, J.B. Bailliere et Fils.

34. Best, C.N., Dale, H.H., Dudley, H.W., and Thorpe, W.V. (1927)
The nature of the vasodilator constituents of certain tissue extracts.
J.Physiol. London 62:397-417

35. Bianchi, P., and Quatrini, M. (1980)
Cimetidine and the Zollinger-Ellison syndrome.
In: "H_2-receptor antagonists in peptic ulcer disease and progress in histamine research. (Ed. Torsoli, A., Luccheli, P.E., Brimblecombe, R.W. p.34-42

36. Binder, H.J., Cocco, A., Crossley, R.J., Finkelstein, W., Font, R., Friedman, G., Groarke, J., Hughes, W., Johnson, A.F., McGuigan, J.E., Summers, R., Vlahcevic, R., Wilson, E.C., and Winship, D.H. (1978)
Cimetidine in the treatment of duodenal ulcer:a multicentre double-blind study.
Gastroenterology 74:380-388

37. Black, J.W., Duncan, A.M., Durant, C.J., Ganellin, C.R., and Parsons, E.M. (1972)
Definition and antagonism of histamine H_2-receptors.
Nature 236:385-390

38. Blackett, R.L., and Johnston, D. (1981)
Cimetidine and duodenal ulcers:can surgery cure the failures?
Gut 22:A434

39. Blackwood, W.S., Maugdal, D.P., Pickard, R.G., Lawrence, D., and Northfield, T.C. (1976)
Cimetidine in duodenal ulcer. Controlled trial.
Lancet 2:174-176

....109

40. Blackwood, W.S., and Northfield, T.C. (1977)
Nocturnal gastric acid secretion:effect of cimetidine and interaction with anticholinergics. In:Proceedings of the Second International Symposium on Histamine H_2-receptor Antagonists. (ed. Burland, W.L. and Simpkins, M.A.). Excerpta Medica Amsterdam:pp124-130.

41. Bodemar, G. and Walan A. (1976).
Cimetidine in the treatment of active duodenal and prepyloric ulcers.
Lancet 2:161-164.

42. Bodemar, G., Norlander, B., and Walan, A. (1977)
Cimetidine in the treatment of active peptic ulcer disease.
In: Cimetidine:Proceedings of the Second International Symposium on Histamine H_2-receptor Antagonists. (Eds. Burland, W.L. and Simpkins, M.A.). Excerpta Medica Amsterdam:pp224-239

43. Bodemar, G. and Walan, A. (1978)
Maintenance treatment of recurrent peptic ulcer by cimetidine.
Lancet 2:403-407

44. Bodemar, G., Gotthard, R., Stom M., Walan, A., Jonsson, B., and Bjurulf, P. (1980)
Socioeconomic aspects of treatment with cimetidine in peptic ulcer disease.
In: "H_2-receptor Antagonists in Peptic Ulcer Disease and Progress in Histamine Research". (eds. Torsoli, A., Lucchelli, P.E., and Brimblecombe, R.W.).
Excerpta Medica Amsterdam:pp59-68

45. Bonfils, S., Lewin, M., Vatier, J., Dubrasquet, M., Bader, J.P. (1968)
Correlation between acid and peptic secretion in man (coefficient K75). (eds. Semb, L.S. and Myren, J.)
The Physiology of Gastric Secretion, Univesitets Farlaget, Oslo: pp 164-173

....110

46. Bovet, D. and Staub, Anne-Marie. (1937)
Action protectrice des ethers phenoliques au ours de l'intoxication histaminique.
Comtes Rendus. Séanc.Soc.Biol. 124:547-549

47. Boyd, E.J.S., Wilson, J.A., and Wormsley, K.G. (1981)
Failure of maintenance therapy in duodenal ulcer.
Gut 22:A880

48. Braun, H. (1899)
Demonstration eines Praforates einer 11 Monate nach der Auhsfuhrung der Gastro-enterostomie entstandenen perforation des jejunum.
Verh.Dtsch.Ges.Chir. 28:94

49. British Medical Journal Leading Article (1948)
Antihistamine drugs in gastric secretion.
Br.Med.J. 2:1028

50. Brittain, R.T., and Daly, M.J. (1981)
A review of the animal pharmacology of ranitidine - a new, selective histamine H_2-antagonist.
Scand.J.Gastroenterol. 16, Suppl.69:1-8

51. Brooks, A.M., Isenberg, J., and Grossman, M.I. (1969)
The effect of secretion, glucagon and duodenal acidification on peptic secretion in man.
Gastroenterology 57:159-162

52. Browning, J.G., and Heathcote, B.V. (1982)
A comparison of the inhibition of centrally stimulated gastric acid and pepsinogen secretion by pirenzepine and cimetidine in the gastric fistula cat.
World Congress of Gastroenterology, Stockholm, Sweden, 1982:pp276

53. Brunner, G. (1982)
Cimetidine resistant ulcers.
In:The Clinical Use of Ranitidine. Glaxo International Symposium, London. Abstract book available from Glaxo, U.K. Ware, Hants:p19

54. Burland, W.L., Duncan, W.A.M., Hesselbo, T., Mills, J.G., and Sharpe, P.C. (1975)
Pharmacological evaluation of cimetidine a new H_2-receptor antagonist in healthy man.
Br.J.Clin.Pharmacol.2:481-486

55. Burland, W.L. (1978)
Evidence for the safety of cimetidine in the treatment of peptic ulcer disease.
In:Proceedings of an International Symposium on Histamine H_2-Receptor Antagonists. (ed. Crautzfeldt, W.)

56. Burland, W.L., Hunt, R.H., Mills, J.G., Milton-Thompson, G.J. (1979)
Drugs of the Decade 1970-1979:cimetidine
Br.J.Pharacotherapy 2:24-40

57. Burland, W.L. , Brunet, P.L., Hunt, R.H., Melvin, M.A., Mills,J.G. Vincent, D., and Milton-Thompson, G.J. (1980)
Comparison of the effects on intragastric acidity of SK&F9299A and two dose regimens of cimetidine.
Hepatogastroenterology Supp (XI Internation Congress of Gastroenterology):259

58. Cargill, J.M., Peden, N., Saunders, J.H.B. and Wormsley, K.G. (1978)
Very long term treatment of peptic ulcer with cimetidine.
Lancet 2:1113-1115

59. Carnot, P., Korskowski, W., and Libert, E. (1922)
L'influence de l'histamine sur la secretion des sucs digestifs chez l'homme Compte Rendus.
Séanc Soc.Biol. Paris 86:575-578

....112

60. Carter, D.C., Forrest, J.A.H., Logan, R.A., Ansell, I., Lidgard, G. Heading, R.C. and Shearman, D.J.C. (1976)
Effect of the histamine H_2-receptor antagonist cimetidine on gastric secretion and serum gastrin during insulin infusion in man.
Scan.J.Gastroenterol. 11:565-570

61. Cavallini, G. Angelini, G., Fralton, S., Ruta, S., Rosa, B., Delorio,M., Savo, L.A. (1982)
Gastrin and exopancreatic function alter a short-term treatment with ranitidine.
World Congress of Gastroenterology, Stockholm, Sweden. No.54:p14

62. Cayer, D., and Ruffin, J.M. (1967)
Effect of Depepsen in the treatment of peptic ulcer.
Ann..N.Y.Acad.Sci. 140:744-746

63. Christiansen, P.M., Svendsen, L.B., Guldager, N., and Christensen,L. (1975)
Pepsin inhibitory pentapeptide on gastric pepsin and hydrochloric acid.
Gut 16:823-824

64. Clarke, R.J., Allen, R.N., and Alexander-Williams, J. (1972)
The effect of retaining antral innervation on the reductions of gastric acid and pepsin secretion after vagotomy.
Gut 13:894-899

65. Cocking, J.B. (1972)
A trial of amylopectin sulphate (SN-263) and propantheline bromide in the long term treatment of chronic duodenal ulcers.
Gastroenterology 62:6-10

66. Code, C.F. (1956)
Histamine and gastric secretion.
In:Histamine. (eds. Wolstenholme, G.E.W. and O'Connor, C.M.) London: 189-219

...113

67. Coggan, D., Lambert, P., and Langman, M.J.S. (1981)
20 years of hospital admissions for peptic ulcer in England and Wales.
Lancet 1:1302-1304

68. Cohen, I.A., Siepler, J.K., Nation, R., Bambeck, C.T. and Nyhus,L.M. (1980)
Relationship between cimetidine plasma levels and gastric acidity in acutely ill patients.
Am.J.Hosp.Pharmacy 37:375-379

69. Colp, R. (1950)
Surgical management of duodenal ulcer.
Surg.Gynae, and Obstet. 91:306-310

70. Committee of Safety of Medicines (1981a)
Current problems. Cimetidine and arthropathy No.7, December.

71. Committee of Safety of Medicines (1981b)
Current Problems. Cimetidine. No.6, July

72. Cook, D.L., and Drill, V.A. (1967)
Pharmacological properties of pepsin inhibitors.
Ann.N.Y.Acad.Sci. 140:724-733

73. Cortet, A., Phillips, S.F., Malagelada, J.R. (1981)
Gastric emptying of lipids after ingestion of a solid-liquid meal in humans.
Gastroenterology 80:922-927

74. Costello, F.T., Fielding, J.D. and Lee, F.I. (1982)
Comparison of ranitidine and cimetidine in short term healing of duodenal ulcer.
Gastroenterology 82:1037

....114

75. Culyer, A.J., and Maynard, A.K. (1980)
Treating ulcers with cimetidine can be more cost effective than surgery.
Medeconomics 57:12-14

76. Domschke, W., Domschke, S., Lux, G., and Demling, L. (1976)
Kinetics of duodenal healing:effect of treatment with cimetidine.
Acta Hepatogastroenterol.23:441-443

77. Döscherholmer, A. (1949)
On the action of the antihistamine agentlergitin on the gastric secretion of hydrochloric acid.
Acta.Med.Scand.135-195-207

78. Dragstedt, L.R., and Owens, F.M. (1943)
Supradiaphragmatic section of the vagus nerves in treatment of duodenal ulcer.
Proc.Soc.Exp.Biol.(N.Y.) 53:152-154

79. Dragstedt, L.R. (1945)
Vagotomy for gastroduodenal ulcer.
Ann.Surg. 53-152-154

80. Duncan, W.A.M. and Parsons, M.E. (1980)
Reminiscences of the development of cimetidine.
Gastroenterology 78:620-625

81. Eckardt, V., (1981)
Cimetidine:twice daily administration in duodenal ulcer - results of a European multicentre study.
In:Cimetidine in the 80's. (ed. Baron, J.H.). Churchill Livingstone Edinburgh:pp14-20

82. Edin, R., Lundberg, J., Terenius, L., Dahlstrom, A.,Hokfelt,T., Kewenter, J. and Ahlman, H. (1980)
Evidence for vagal enkephalinergic neural control of the feline pylorus and stomach.
Gastroenterology 78:492-497

...115

83. Edwards, C.R.W., and Riley, A.J. (1981)
A review of the endocrine effects of rantitidine:comparison with cimetidine. In: The Clinical Use of Ranitidine. International Symposium. Barbican Centre, London. Abstracts from Glaxo, Ware: p.27

84. Elder J.B., Gillespie, I.E., Ganguli, P.C., Delamere, W.I. and Gregory H. (1975)
Effect of urogastrone in the Zolliner-Ellison syndrome.
Lancet 2:424-427

85. Elder, J.B., Ganguli, P.C., and Gillespie, I.E. (1979)
Cimetidine and gastric cancer.
Lancet 1:1005-1006

86. Emas, S., and Grossman, M.I. (1967)
Effect of truncal vagotomy on acid and pepsin responses to histamine and gastrin in dogs.
Am.J.Physiol.212:1007

87. Emmelin, N., and Kahlson, G.S. (1944)
Histamine as a physiological excitant of gastric acid secretion.
Acta.Physiol.Scan. 8:289-304

88. Emmelin, N. and Frost, J. (1947)
The effect of β-dimethyl - aminoethyl - benzylolryl - ether hydrochloride on histamine-induced gastric secretion in the cat.
Acta Physiol.Scand. 13:75-80

89. Feldman, M. Richardson, C.T., and Fordtran, J.S. (1980)
Effect of sham feeding on gastric acid secretion in healthy subjects and duodenal ulcer patients:evidence for increased basal vagal tone in some ulcer patients.
Gastroenterology 79:796-800

....116

90. Fineberg, H.V. and Pearlman, L.A. (1981)
Surgical treatment of peptic ulcer in the United States.
Lancet 1:1305-1306

91. Fordtran, J.B. and Walsh, J.H. (1973)
Gastric acid secretion rate and buffer content of the stomach after eating. Results in normal subjects and in patients with duodenal ulcer.
J.Clin.Invest. 52:645-657

92. Forrest, J.A.H., Fettes, M., McLoughlin, G., Heading, R.C. (1978)
The effect of long term cimetidine on gastric acid secretion, serum gastrin and gastric emptying.
In: Cimetidine, The Westminster Hospital Symposium. (ed.Wastell,C. and Lance P). Churchill Livingstone 57-65

93. Fritsch, W.P., Scholten, T., Muller, J. and Hengels, K.J. (1980)
Newly developed drugs:modes of action and clinical experience.
In:"A symposium on recent advances in the pathophysiology and etiology of duodenal ulcer". (eds, Holter-Muller, K.H. and Malagdelada, J.R.) Excerpta Medica Amsterdam:pp427-448

94. Gabryelewicz, A., Sarosiek, J., Laszewicz, W. and Piotrowski, J. (1982)
The effect of combined application of ranitidine (RN/pirenzepine/PC) on gastric mucus, hydrochloric acid and pepsin secretion stimulated with peptavalon/P/in duodenal ulcer/DU/patients.
World Congress of Gastroenterology, Stockholm, Sweden 1982:No.52: p13

95. Galambos, A. (1926)
Direct examination of the gastric juice. A new functional test.
Arch.Intern.Med. 38:654-662

....117

96. Gardham, J.R.C., Hassan, M.A., and Hobsley, M. (1968)
The recognition and measurement of pyloric reflux in aspirated gastric juice.
Br.J.Surg. 55:865

97. Garner, A. and Flemstrom, G. (1978)
Gastric bicarbonate secretion in the guinea pig.
Am.J.Physiol.234:E535-E541

98. George, J.D. (1968)
New clinical method for measuring the rate of gastric emptying: the double sampling test meal.
Gut 9:237-242

99. Gibson, R., Hirschowitz, B.I., and Hutchison, G. (1974)
Actions of metiamide, an H_2-histamine receptor antagonist on gastric H^+ and pepsin secretion in dogs.
Gastroenterology 67:93-99

100. Gillespie, I.E. (1982)
When vagotomy fails.
Br.Med.J. 284:1815-1816

101. Glass, G.B.J. (1967)
Current status of the glandular mucoprotein and mucoprotease fractions of the gastric mucin, a review of 15 years progress in this area.
Ann.N.Y.Acad.Sci. 140:804

102. Gledhill,T., Mills, J.G., Clancy, A., Buck, M., Hunt, R.H., and Burland, W.L. (1982)
Nocturnal acid output and 24 hour intragastric acidity in duodenal ulcer patients are significantly inhibited by an evening dose of SK&F 93479.
Gut 23:A455

103. Gouldong, A.M., Borsook, H., and Wasteneys, H. (1927)
Autodestruction of pepsin in relation to ionization.
J.Gen.Physiol. 10:451-467

104. Graffried, V.B., Pozo, D.E., Roubieck, J., Krebs, E., Poldinger, W., Burmeister, P. and Kerp, L.
Effects of synthetic enkephalin analogue FK33-824 in man.
Nature 272:729-730

105. Gray, G.R., McKenzie, I., Smith, I.S., Crean, G.P., and Gillespie, G. (1977)
Oral cimetidine in severe duodenal ulceration:a doublt-blind controlled trial.
Lancet 1:4-7

106. Gray, S.P., and Billings, J.A. (1982)
A new automated pepsin assay.
Submitted for publication

107. Greenspan, R., Levy, R., and Necheles, H. (1951)
Gastric ulcer with true acidity and pain relief with alkalis.
Gastroenterology 17:420-424

108. Gregory, R.A., and Ivy, A.C. (1941)
The humoral stimulation of gastric secretion.
Quart.J.Physiol.31:111-128

109. Griffith, C.A. and Harkins, H.N. (1957)
Partial gastric vagotomy:an experimental study.
Gastroenterology 32:96-102

110. Griffith, G.H., Owen, G.M., Kirkman, S. and Shields, R. (1966)
Measurement of rate of gastric emptying using chromium 51.
Lancet 1:1244-1245

....119

111. Grossman, M.I. (1967)

Neural and hormonal stimulation of gastric secretion of acid. In:Handbook of Physiology, section 6, Alimentary Canal Vol.12 (ed. Code, C.F., Washington):pp835-863

112. Grossman, M.I. (1980)

Peptic Ulcer:the pathophysiological background.

Scand.J.Gastroenterol. 15:7-16

113. Guldvag, I. (1980)

Vagally innervated and denervated gastric pouch in one and the same dog.

Scand.J.Gastroenterol. 15:921-928

114. Guldvag, I. and Berstad, A. (1982_a)

H_2-mediated inhibition of pepsin secretion.

World Congress of Gastroenterology, Stockholm, Abstract No. 1093 p.275

115. Guldvag, I. and Berstad, A. (1982)

The pepsin test for completeness of vagotomy. Comparison of pepsin versus acid response.

World Congress of Gastroenterology, Stockholm. Abstract No.69: p.18

116. Gusaldi, M., Testori, P.A., Fesce, E., Ballarin, E., and Tittobello, A. (1980)

Behaviour of gastric mucus during pirenzepine treatment:a double-blind controlled study versus cimetidine.

Current Therapeutic Research 27:714-718

117. Guth, P.H, Bauman, H., Grossman, M.I., Aures, D. and Elachoff,J. (1978)

Measurement of gastric mucosal blood flow in man.

Gastroenterology 74:831-834

...120

118. Hammer, R., and Koss, F.W. (1979)
The pharmacokinetic profile of pirenzepine.
Scan.J.Gastroenterol.14, Suppl.57:1-6

119. Hancock, B.D., Bowen-Jones, E., Dixon, R., Testa, T., Dymock, I.W. Cowley, D.J. (1974)

120. Hartzell, J.B. (1929)
Effect of section of vagus nerves on gastric acidity.
Am.J.Physiol.91:161-171

121. Hassan, M.A., Gardham, J.R.C. and Hobsley, M. (1969)
Evaluation of errors of gastric secretion studies.
Br.J.Surg. 56:384

122. Hassan, M.A., and Hobsley, M. (1970)
Positioning of the subject and of nasogastric tube during a gastric secretion study.
Br.Med.J. 1:458-460

123. Heading, R.C., Tothill, P., McLoughlin, G.P. and Shearman, D.J.C. (1976)
Gastric emptying rate measurement in man.
Gastroenterology 71:45-50

124. Heading, R.C., Logan, R.F.A., McLoughlin, G.P., Lidgard, G. and Forrest, J.A.H. (1977)
Effect of cimetidine on gastric emptying.
In: Cimetidine, Proceedings of the Second International Symposium on Histamine H_2-receptor Antagonists. (eds. Burland, W.L. and Simkins, M.A.
Excerpta Medica, Amsterdam:pp145-152

125. Heading, R.C., Blackwell, J.N., and Cameron, E.W.J. (1981)
Long term management of reflux patients.
In: Cimetidine in the 80's. (ed. Baron, J.H.) Churchill Livingstone Edinburgy:pp172-181.

...121

126. Helmer, O. and Fouts, P.J. (1937)
Gastric analysis methods.
Am.J.Clin,Pathol. 7:41-50

127. Henry, D.A., MacDonald, I.A., Kitchingman, G., Bell, G.D. and Langman, M.J.S. (1980)
Cimetidine and ranitidine:comparison of effects on hepatic drug metabolism.
Br.Med.J. 281-775-777

128. Hetzel, D.J., Hansky, J., Shearman, D.J.C., Korman, M.G., Hecker,R., Taggart, G.J., Jackson, R. and Gabb, B.W. (1978)
Cimetidine treatment of duodenal ulcers. Short term clinical trial and maintenance study.
Gastroenterology 74:389-392

129. Hirschowitz, B.I., and London, J.A. (1955)
Studies of the secretion of acid, water and pepsinogen by the human stomach.
J.Lab.Clin.Med.46:826-827

130. Hirschowitz, B.I. (1957)
Pepsinogen, its origins, secretion and excretion.
Physiol.Reviews 37:475-511

131. Hirschowitz, B.I. (1967)
Control of pepsinogen secretion.
Ann.N.Y.Acad.Sci.140:709

132. Hirschowitz, B.I. and Gibson, R. (1973)
Effects of burinamide and of metiamide on gastric acid and pepsin secretion in the dog.
In: International Symposium on Histamine H_2-receptor Antagonists. (eds. Wood, C.J., and Simpkin, M.A.) Smith, Kline & French, Welwyn Garden City:pp273-290

...122

133. Hirschowitz, B.I., Sachs, G. and Hubchison, G. (1973)
Lack of potentiation or synergism between histamine and pentagastrin in the fistula dog.
Am.J.Physiol. 224:509-513

134. Hobsley, M. and Silen, W. (1969)
Use of an insert marker (phenol red) to improve accuracy in gastric secretion studies.
Gut 10:797-795

135. Hollander, F. (1946)
The insulin test for the presence of intact nerve fibres after vagal operations for peptic ulcer.
Gastroenterology 7:607-614

136. Hollander, D. (1981)
Efficacy of sucralfate for duodenal ulcers:a multicentre double-blind trial.
J.Clin.Gastroent. 3:153-157

137. Holtermuller, K.H. and Malagelada, J.R. (1980)
Advances in ulcer disease. Proceedings of a symposium on the pathogenesis and therapy of ulcer disease.
Excerpta Medica Amsterdam:p389

138. Horowitz, M.I. (1967)
Chemistry of the secretion layer.
Am.N.Y.Acad.Sci. 140:784-797

139. Humphrey, C.S., Johnston, D., Walker, B.E., Pulvertaft, C.N., and Goligher, J.C. (1972)
Incidence of dumping after truncal and selective vagotomy with pylorplasty and highly selective vagotomy without drainage procedure.
Br.Med.J. 3:785-788

...123

140. Hunt, J.N., (1950)
An interpretation of histamine and insulin tests on patients with peptic ulceration.
Lancet ii:397-400

141. Hunt, J.N., (1950)
An interpretation of the histamine test of gastric secretion.
Gastroenterology 16:231-240

142. Hunt, R.H., Mills, J.G., Beresford, J., Billings, J.A., Burland, W.L., and Milton-Thompson, G.J. (1980)
Gastric secretory studies in humans with impromidine (SK&F92676)- a specific histamine H_2-receptor agonist
Gastroenterology 78:505-511

143. Hunt, R.H., Vincent, D. Kelly, J.M., Perry, M., Milton-Thompson,J.G. (1980)
Comparison of medical and surgical reduction in intragastric acidity in duodenal ulcer.
Gut 21:A455

144. Hunt, R.H. (1981)
Nonresponders to cimetidine 1.
In: Cimetidine in the 80's. (ed. Baron, J.H.), Churchill Livingstone, Edinburgh:pp34-41

145. Hunt, R,H. (1982a)
Peptic ulcer in the Royal Navy.
J.Roy.Naval Med.Service 67:125-130

146. Hunt, R.H. (1982b)
Use and abuse of H_2-receptor antagonists.
J.Roy.Col.Phys.Lond. 16:33-39

147. Ingolby, C.J.H., Man, W. and Spencer, J. (1982)
Histamine is not the final common pathway for gastric acid secretion.
World Congress of Gastroenterology, Stockholm, Abstract No.1074:p275

....124

148. Ippoliti, A.F., Sturdevant, R.A.L., Isenberg, J.I., Binder, M., Camacho, R., Cano, R., Cooney, C., Kline, M.M., Koretz, R.L., Meyer, J.H., Samloff, I.M., Schwabe, A.D., Strom, E.A., Valenzuela, J.E., and Wintroub, R.H. (1978)
Cimetidine versus intensive antacid therapy for duodenal ulcer: a multicentre trial.
Gastroenterology 74 (Suppl):393-395

149. Isenberg, J.I., Spector, H., Hootkin, L.A., and Pitcher, J.C. (1971)
An apparent exception to Schwarz's dictum "no acid - no ulcers".
N.Eng.J.Med. 285:620

150. Ivey, K.J. (1975)
Anticholinergics:do they work in peptic ulcer?
Gastroenterology 68:154-166

151. Janowicz, H.D. and Hollander, F. (1951)
Jejunal ulcer in the presence of gastric achylai - a case report.
Gastroenterology 17:425-430

152. Janowitz, H.D. and Hollander, F. (1952)
The basal secretion of pepsin by the human stomach.
J.Clin.Invest. 31:338-340

153. Jaup, B.H. (1981)
Studies on the mode of action of pirenzepine in man with special reference to its anticholinergic muscarinic properties.
Scand.J.Gastroenterol. 16 (Suppl) 68:1-26

154. Johnston, D. and Wilkinson, A.R. (1970)
Highly selective vagotomy without a drainage procedure in the treatment of duodenal ulcer.
Br.J.Surg. 57:289-296

155. Johnston, D.H. and McGraw, B.H. (1958)
Gastric analysis - evaluation of collection techniques.
Gastroenterology 35:512-516

.....125

156. Johnson, L.R. (1971)
Control of gastric secretion:no room for histamine?
Gastroenterology 61:106-118

157. Johnson, L.R. (1972a)
Regulation of pepsin secretion by topical acid in the stomach.
Am.J.Physiol.223:847-850

158. Johnson, L.R. (1972b)
Pepsin stimulated by topical hydrochloric and acetic acids.
Gastroenterology 62:33-38

159. Kapadia, C., and Donaldson, R.M. (1978)
Macromolecular secretion by isolated gastric mucosa:fundamental differences in pepsin and intrinsic factor secretion.
Gastroenterology 72:535-539

160. Kasbekar, D.K., Jensen, R.T. and Gardner, J.D. (1982)
Stimulation of pepsinogen secretion from isolated rabbit gastric glands.
Gastroenterology 82:1097

161. Kay, A.W. (1953)
Effect of large doses of histamine on gastric secretion of hydrochloric acid.
Br.Med.J. 2:77-80

162. Keenan, R.A., Hunt, R.H., Vincent, D., Wright, B., Milton-Thompson,G.J. (1978)
The case for high dose antacid therapy in duodenal ulcer.
Gut 19:A974

163. Kerr, G.D. (1981)
Cimetidine:twice daily administration in duodenal ulcer - results of a UK and Ireland multicentre study.
In:Cimetidine in the 80's. (ed. Baron, J.H.). Churchill Livingstone, Edinburgh:pp9-13

....126

164. Kirkpatrick, P.M. and Hirschowitz, B.I. (1980)
Duodenal ulcer with unexplained marked basal gastric acid hypersecretion.
Gastroenterology 79:4-10

165. Kishi, S., Seki, H., Kilamura, Y., and Mori, H. (1978)
Levels of gastric pepsin secretion in relation to clinical course of duodenal ulcer.
Tokuishima J.Exp.Med. 25:59-66

166. Klotz, A.P. and Duvall, M.R. (1957)
The laboratory determination of pepsin in gastric juice with radioactive iodinated albumin.
J.Lab.&Clin.Med. 50:753-757

167. Knigge, U., Wollesen, F., Dejgarrd, A., Thuesen, B. and Christiansen, P.M. (1981)
Comparison between dose response of prolactin, thyroid stimulating hormone and growth hormone to two different histamine H_2-receptor antagonists in normal men.
Clinical Endocrinology 15:585-592

168. Kondo, T. and Magee, D.F. (1977)
The secretion of pepsin.
J.Physiol.(Lond) 270:29-36

169. Konturek, S.J., Kwiecien, N., Obtulowicz, W., Scurierczek, J., Olesky, J. and Coy, D.H. (1982)
Effects of enkephalin on gastric secretory and plasma hormone responses to cephatic stimulation in man.
World Congress of Gastroenterology, Stockholm. Abstract No.468: p118

170. Korn, E.R., and Foroozan, P. (1974)
Pyloric channel ulcer with betazole-fast achlorhydria.
Gastroenterology 67:1248-1249

....127

171. Lance, P. and Gazzard, B.G. (1982)
A controlled trial of cimetidine for the symptomatic treatment of duodenal ulcers.
Gastroenterology 82:1111

172. Langman, M.J.S. (1978)
Clinical features of non-ulcer dyspepsia.
In: Cimetidine. The Westminster Hospital Symposium. (eds. Wastell,C. and Lance, P.). Churchill Livingstone, Edinburgh:pp107-111

173. Langman, M.J.S. (1982)
What is happening to peptic ulcer?
Br.Med.J. 284:1063-1064

174. Langman, M.J.S., Henry, D.A., and Ogilive, A. (1981)
Ranitidine and cimetidine for duodenal ulcer.
Scand.J.Gastroenterol. 16(Suppl.169):115-117

175. Latarjét, A. (1922)
Résection des nerfs de l'estomac. Technique opératoire. Resultats cliniques.
Bull.Acad.Méd. Paris 87:681-691

176. Lennard-Jones, J.E., and Barbouris, N. (1965)
Effect of different foods on the acidity of the gastric contents in patients with duodenal ulcer.
Gut 6:113-117

177. Leube, W.O. (1868)
Beitrage zur Kenntniss des Dunndarmsafts und seiner Wirkungen, Erlangen.
Druck Von E.Th.Jacob. 20:4

178. Levin, E. Kirsner, J.B. and Palmer, W.L. (1950)
The continuous twelve-hour nocturnal gastric secretion in normal individuals and in patients with duodenal ulcer after a 24 hour fast.
Gastroenterology 15:454-457

....128

179. Linde , S. (1950)
Studies on the stimulation mechanism of gastric secretion.
Acta Physiol.Scand. 21 (Suppl.4):1-92

180. Lombardo, L. (1982)
Reversible amenorrhoea after ranitidine treatment.
Lancet 1:224

181. Londong, W., Londong, V., Weber, T.H., and VonWerder, K. (1980)
Interactions of an antimuscarinic and an H_2-receptor antagonising drug in man.
Gut 21:A451

182. Longstreth, F.G., Malagelada, J.R. and Go, V.L.W. (1975)
Effect of cimetidine on gastric functions during and after digestion of ordinary solid meals in duodenal ulcer.
Gastroenterology 68:942

183. Longstreth, G.F., Go, V.L.W., and Malagelada, J.R. (1976)
Cimetidine suppression of nocturnal gastric secretion in active duodenal ulcer.
N.Eng.J.Med. 294:801-804

184. Macleod, I.B.
Duodenal ulcer - the surgeons dilemma
J.Roy.Coll.Surg.Edin. 12:285-307

185. Mario, F.D., Plebani, M., Vionello, F., Farini, R., Giordaro, A., Scalaboir, G., Coriotti, G., and Naccova, R. (1980)
Serum pepsinogen in normal subjects and in peptic ulcer and its modifications after ranitidine treatment.
Gut 21:A930

186. Marks, I.N., Wright, J.P., Denyer, M., Garish, J.A.M. and Lucke, W. (1980)
Comparison of sucralfate with cimetidine in the short term treatment of chronic peptic ulcers.
A.S.Med.J. 57:567-573

...129

187. Martin, D.F., Hollander, D., May, S.J. Ravenscroft, M.M., Tweedle, D.E.F., and Miller, J.P. (1981)
Difference in relapse rates of duodenal ulcer after healing with cimetidine or tripotassium dicitratobismuthate.
Lancet 1:7-10

188. Martin, F., Farley, A., Gagnan, M. and Bensemana, D. (1982)
Comparison of the healing capacities of sucralfate and cimetidine in the short term treatment of duodenal ulcer:a doublt-blind randomised trial.
Gastroenterology 82:401-405

189. Maybury, N.K. and Carr-Locke, D.L. (1980)
The value of the new interpretation of the insulin test in prediciting duodenal ulcer relapse after treatment with cimetidine.
Br.J.Surg.67:315-317

190. Mayo, W.J. (1902)
Complications following gastroenterostomy.
Ann.Surg. 36:231-244

191. McGuigan, J.E. (1981)
A consideration of the adverse effects of cimetidine.
Gastroenterology 80:181-192

192. McKay, A.J. and McArdle, C.S. (1981)
Cimetidine and perforated peptic ulcers.
Gut 22:A880

193. McWhinnie, D.L., Gray, G.R.., Smith, I.S., and Gillespie, G. (1980)
Cimetidine or surgery for severe duodenal ulcer dyspepsia? Results of a three to four year follow-up.
Gut 21:A922

194. Mignon, M., Vallot, T., Galniche, J.P., Dupas, J.L. and Bonfils, S. (1980)
Interest of a combined antisecretory treatment, cimetidine and pirenzepine in the management of severe forms of Zollinger-Ellison syndrome.

195. Milton-Thompson, G.J., Lightfoot, N.F., Ahmet, Z., Hunt, R.H., Barnard, J., Bavin, P.M.G., Brimblecome, R.W., Darkin, D.W., Moore, P.J. and Viney, N. (1982)
Intragastric acidity, bacteria, nitrite and N-nitroso compounds before, during, and after cimetidine treatment.
Lancet 1:1091-1095

196. Moersch, R.U., Rivos, A.B. and Morlock, (1946)
Some results of the gastric secretory response of patients having duodenal ulcer noted during the administration of benadryl.
Gastroenterology 7:91-99

197. Magee, D.F., and Hu, C.Y.
Heidenhein pouch distension as a stimulus for acid and pepsin secretion.
Ann.Surg. 182:121-123

198. Mohammed, R., Mitchell, K.G. and Mackay, C. (1981)
The treatment of "cimetidine resistant" peptic ulcers by ranitidine hydrochloride:a new histamine H_2-receptor antagonist.
Curr.Med.Res.Opin. 7:523-525

199. Moody, F.G., McGreevy, J., Zalewsky, C., Cheung, L.Y., and Simons, M. (1978)
The cytoprotective effect of mucosal blood flow in experimental erosive gastritis.
Acta.Physiol.Scand. Special Suppl:pp35-43

200. Moore, E.W. and Scarlata, R.W. (1965)
The determination of gastric acidity by the glass electrode.
Gastroenterology 49:178-188

201. Moore, J., Howe, J.P., Dundee, J.W., Johnston, J.R., and McCaughey, W. (1981)
Cimetidine in anaesthetic practice.
In: Cimetidine in the 80's. (ed. Baron, J.H.). Churchill Livingstone, Edinburgh:pp215-221

....131

202. Morgan, A.G., McAdam, W.A.F., Pacsoo, C., Walker, B.E. and Simmons, A.V. (1978)
Cimetidine:an advance in gastric ulcer treatment.
Br.Med.J. 2:1323-1326

203. Morgan, A.G., McAdam, W.A.F., and Pacsoo, C. (1981)
A comparison between ranitidine and caved S in duodenal ulcer treatment.
International Symposium , Barbican Centre, London. Abstracts available from Glaxo Group Research Limited, Ware, England

204. Morgan, A.G., McAdam, W.A.F., Pacsoo, C. and Dornborough, A. (1982)
A comparison between cimetidine and caved S in the treatment of gastric ulceration and subsequent maintenance therapy.
Gut 23:545-551

205. Moynihan, Sir Berkeley (1917)
The institutes of surgery. A historical review.
Br.Med.J. 171-175

206. Muller-Lissner, S.A., Sonnenberg, A., Eichenberger, P. and Blun, A.L. (1981)
Effect of ranitidine on gastric acid and pepsin secretion following sham feeding.
Scand.J.Gastroenterol.69:27-31

207. Muscroft, T.J., Youngs, D.J., Burdon, D.W. and Keighley, MRB(1981)
Cimetidine is unlikely to increase formation of intragastric nitroso-compounds in patients taking a normal diet.
Lancet 1:408-410

208. Northfield, T.C., Zentler-Munro, P.L., Fitzpatrick W.J. and Fine, D.R. (1981)
Treatment of pancreatic and ileectomy steatorrhoea.
In:Cimetidine in the 80's. (ed.Baron, J.H.).Churchill Livingstone, Edinburgh:pp208-214

....132

209. Olbe, L.P., Ridley, P.T. and Uvnas, B. (1968)
Effect of gastrin and histamine on vagally induced acid and pepsin secretion in antrectomised dogs.
Acta Physiol.Scand. 72:492

210. Pavlov, I.P. (1910)
The work of the digestive glands.
Griffin

211. Payne, C.R., Ackrill, P. and Ralston, A.J. (1982)
Acute renal failure and rise in alkaline phosphatase activity caused by cimetidine.
Br.Med.J. ii:100

212. Payne, R.A. and Kay, A.W. (1962)
The effect of vagotomy on the maximal acid secretory response to histamine in man.
Clin.Sci.22:373-382

213. Péan, J. (1879)
De l'Ablation des Tunews de l'Estomac par la Gastrectomie.
Gaz.Hop.52:473-475

214. Peden, N.R., Boyd, E.J.S., Browning, M.C.K., Saunders, J.H.B., and Wormsley, K.G. (1981)
Effects of two histamine H_2-receptor blocking drugs on basal levels of gonadotrophins, prolactin, testosterone and oestradial - 17β during treatment of duodenal ulcer male patients.
Acta.Endocrinologica 96:564-568

215. Polak, J.M., Sullivan, S.N., Bloom, S.R., Facer, P., and Pearse, A.G.E. (1977)
Enkephalin like immunoreactivity in the human gastrointestinal tract.
Lancet 1:972-974

...133

216. Pelikon, V., Horcicka, V, and Komenda, S., (1969)
Diverse methodes pour l'exploration de la secretion gastrique an caus de l'ulcere du duodenum
Acta Gastroent.Belg. 32:707-718

217. Peter, P., Fritsch, W.P., Nieschlag, E., Wienbeck, M. and Strohmeyer, B. (1977)
Cimetidine in the treatment of duodenal ulcer.
In:Cimetidine Proceedings of the Second International Symposium on Histamine H_2-receptor Antagonists. (ed.Burland, W.L. and Simkins, M.A.)
Excerpta Medica Amsterdam:pp254-259

218. Peterson, W.L., Sturdevant, R.A.L., Franki, H.D., Richardson, C.T., Isenberg, J.I., Elashoff, J.D., Sernes, J.G., Gross, R.A., McCallum, R.W., and Fordtran, J.S. (1977)
Healing of duodenal ulcer with an antacid regimen.
N.Eng.J.Med. 297:341-345

219. Pikkarainen, P., Vuoristo, M., and Torpila, S.
Ulcer healing and serum pepsinogen I in cimetidine and glycopyrrolate treated duodenal ulcer patients.
Ann.Clin.Res. 13:81-84

220. Piper, D.W., and Fenton, B.H., (1964)
Antacid therapy of peptic ulcer Part II. An evaluation of antacids in vitro.
Gut 5:585-589

221. Playle, A.C., Gunning, S.R. and Llewellyn, A.F. (1974)
In vitro antacid and antipeptic activity of hydrotalcite.
Pharm.Acta.Helv. 49:298-302

222. Pollard, H.M. and Augur, N.A. (1968)
Peptic ulcer over the past 100 years.
Practitioner 201:139-146

....134

223. Popielski, L. (1920)
β imidazolathylamin und die organestrakte erster und zweiter teilen.
Pflugers.Arch.ges.Physiol.178:214-259

224. Pounder, R.E. Williams, J.G., Russell, R.C.G.., Milton-Thompson,G.J. and Misiewicz, J.J. (1976)
Inhibition of food stimulated gastric acid secretion by cimetidine.
Gut 17:161-168

225. Pounder, R.E., Williams, J.G., Milton-Thompson, G.J., and Misiewicz, J.J. (1976)
Effect of cimetidine on 24 hour intragastric acidity in normal subjects.
Gut 17:133-138

226. Pounder, R.E., Hunt, R.H., Vincent, S.H., Milton-Thompson, G.J. and Misiewicz, J.J. (1977)
Twenty-four hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer during oral administration of cimetidine and atropine .
Gut 18:85-90

227. Pounder, R.E. (1981)
Maintenance treatment, part 3 - cost effectiveness.
In: Cimetidine in the 80's. (ed. Baron, J.H.). Churchill Livingstone Edinburgh:pp89-94

228. Price, C. and Elder, J.B., (1981)
Effect of cimetidine on peptic ulcer surgery in the north-west of England.
Gut 22:A879

229. Prout, W. (1824)
On the nature of the acid and saline matters usually existing in the stomach of animals.
Philosophical Transactions of the Royal Society 1:45-48

....135

230. Raufman, J.P., Kasbekar, D.K., Jensen, R.T. and Gardner, J.D. (1982)
Secretin and VIP potentiate cholinergic stimulation of pepsinogen secretion from dispersed gastric glands.
Gastroenterology 82:1155

231. Réaumur, R.A.F. (1756)
Sur la digestion des oiseaux.
Memoires de l'Academie Royale des Sciences :pp 266-307; 461-495

232. Reed, P.I. and Davies, W.A. (1978)
Endoscopic assessment of a duodenal ulcer healing agent (Duogastrone).
In: Peptic Ulcer Healing; recent studies on carbenoxolone.
(eds. Avery-Jones, Sir Francis and Langman, M.J.S.) MTP Press Ltd.
International Medical Publishers, Lancaster, England:pp101-111

233. Rees, W.D.A. and Turnberg, L.A. (1982)
Mechanisms of gastric mucosal protection:a role for the 'mucus-bicarbonate' barrier.
Clin.Sci. 62:343-348

234. Richardson, C.T. (1978)
Effect of H_2-receptor antagonists on gastric acid secretion and serum gastrin concentrations.
Gastroenterology 74:366-370

235. Roberto, D.M.P., Nicola, D.I. and Sergio, D. (1982)
Combined antisecretory treatment cimetidine and pirenzepine in severe peptic ulcers.
World Congress of Gastroenterology, Stockholm. Abstract No. 59: p.15

236. Roland, M. Berstad, A. and Liavag, I. (1974)
Acid and pepsin secretion in duodenal ulcer patients in response to graded doses of pentagastrin and carbacholine before and after proximal gastric vagotomy.
Scand.J.Gastroenterol.9:511-518

....136

237. Roley-Jones, D., Flind, A.C. and Blackhouse, J.N. (1980)
The safety of cimetidine:a continuing assessment.
Proceedings of Second International Symposium on Cimetidine (Tagamet).
(eds. Dress, A., Barbier, F., Harrengt, C., Tijtgat, G.N.)
Excerpta Medica Amsterdam:pp78-88

238. Rosato, E.F., Rosato, F.E. and MacFadyen, B. (1971)
Effect of truncal vagotomy on acid and pepsin responses to histamine in duodenal ulcer subjects.
Ann.Surg.173:63-66

239. Ruddell, W.S.J., Axon, A.T.R., Findlay, J.M.,Bartholomew, B.A. and Hill, M.J., (1980)
Effect of cimetidine on the gastric bacterial flora.
Lancet 1:672-674

240. Saunders, J.H.B., Cargill, J.M., and Wormsley, K.G. (1977)
Effects of cimetidine and poldine on nocturnal gastric secretion in duodenal ulcer.
Digestion 15:452-456

241. Schiffrin, M.J. (1940)
Production of the experimental jejunal ulcer.
Proc.Soc.Exp.Biol.Med. 45:594-595

242. Schiffrin, M.J., and Warren, A.A. (1942)
Some factors concerned in the production of experimental ulceration of the GI tract in cats.
Am.J.Dig.Dis 9:205-209

243. Schofield, B. (1959)
The inhibition of pepsin output in separated gastric pouches in dogs following feeding and its correlation with motility changes.
Gastroenterology 37:169

....137

244. Scholton, T., Schuchert, A. Fritsch, W.P., Muller, J.E., and Hagels, J.J. (1982)
Inhibition of postprandial nocturnal gastric acid secretion by pirenzepine, ranitidine and combined therapy.
World Congress of Gastroenterolgy, Stockholm. Abstract No.51:p13

245. Schoon, I.M. and Olbe, L. (1978)
Inhibitory effect of cimetidine on gastric acid secretion vagally activated by physiological means in duodenal ulcer patients.
Gut 19:27-31

246. Schutz, E. (1982)
Behandlung cimetidin resistenter ulcera duodeni mit dem neuen H_2-receptor antagonisten ranitidin.
Therapiewocke 32:2077

247. Schwann, T. (1836)
Ueber das Wesen des Verdauungsprocessess.
Mullers Arch.Anat.Physiol.:pp90-138.

248. Schwartz, K. (1910)
Ueber penetrierende Magen - und Jejualgeschure.
Bruns.Beitr.klin.Chir. 67:96-128

249. Serlin, M.J. (1981)
Lack of interaction with other drugs.
IN: The Clinical Use of Ranitidine. International Symposium, London.

250. Sheers, R., and Roberts, N. (1981)
The effect of ranitidine and cimetidine on pentagastrin and insulin stimulated gastric secretion.
Scand.J.Gastroenterol. 16 (Supple.69):51-57

251. Sol, A.H. (1978)
Effects of the H_2 antagonists on histamine action and interaction with gastrin in isolated parietal cells.
Gastroenterology 74:355

....138

252. Sol, A.H., Amirian, D.A., Thomas, L. and Ayalan, A. (1982)
Secretagogue stimulation of pepsinogen release by canine chief cells in primary monolayer culture.
Gastroenterology 82:1184

253. Sonnenberg, A. Muller-Lissner, S.A. Vogel, E., Schmid, P., Gonvers, J.J., Peter, P., Strhmeyer, G., and Blum, A.L. (1981)
Predictors of duodenal ulcer healing and relapse.
Gastroenterology 81:1061-1067

254. Spallanzani, L. (1783)
Experiences sur la digestion de l'homme et de differentes especes d'animaux.
Trans.J.Senebier.Barthelemi Chiral, Geneva

255. Spence, R.W., McCormick, D.A., Oliver, J.M. and Celestin, L.R. (1978)
The effect on serum gastrin of withdrawal of cimetidine after one year's treatment.
In: Cimetidine, The Westminster Hospital Symposium (eds. Wastell,C. and Lance, P.) Chucrhill Livingstone, Edinburgh:pp153-166

256. Spencer, J., Puckett, R., and MacFarland, R. (1962)
Seasonal variations in gastric free HCl production.
Am.J.Dig.Dis. 7:394-400

257. Spencer, H. and Lender, M. (1979)
Adverse effects of aluminium containing antacids on mineral metabolism.
Gastroenterology 76:603-606

258. Sperazara, V., Basso, N. Bagarani, M., Fiorani, S., Bianchi, E., and Matera, A. (1980)
Prophylaxis of acute gastroduodenal mucosal lesions:a controlled trial.In:H_2-receptor Antagonists in Peptic Ulcer Disease and Progress in Histamine Research. (eds. Torsoli, A., Lucchelli, P.E. and Brimblecombe, R.W.) Excerpta Medica Amsterdam:pp155-158

.....139

259. Stage, J.G., Stadil, F., Fischerman, K. (1971)
New aspects in the treatment of Zollinger-Ellison syndrome.
In: Proceedings of an International Symposium on Histamine H_2-receptor Antagonists. (ed. Creutzfeldt, W.) Excerpta Medica Amsterdam:pp13

260. Stalsberg, H., Taksdal, S., (1971)
Stomach cancer following gastric surgery for benign conditions.
Lancet ii:1175-1177

261. Sullivan, S.N., Corke, M. and Darwish, R. (1982)
Inhibition of basal and stimulated gastric acid secretion by an enkephalin analogue.
Am.J. Gastroenterol. 77:360-362

262. Stubbs, W.A., Delitala, G., Jones, A., Jeffcoate, J., Edwards, C.R.W. Ratter, S.J., Besser, G.M., Bloom, S.R., Alberti, K.G.M.M. (1978)
Hormonal and metabolic response to an enkephalin analogue in normal man.
Lancet 2:1225-1227

263. Sun, D.C.H. and Ryan, M.L. (1970)
A controlled study on the use of propantheline and amylopectin sulphate (SN-263) for recurrences in duodenal ulcer.
Gastroenterology 58:756-761

264. Taylor, W.H. (1970)
Pepsins of patients with peptic ulcer.
Nature 227:76-77

265. Tewani, S.N., and Trenbalowicz, F.C. (1968)
Some experience with degylcyrrhizinated liquorice in the treatment of gastric and duodenal ulcers with special reference to its spasmolytic effect.
Gut 9:48-51

....140

266. Thjodleifsson, B. and Wormsley, K.G. (1975)
Aspects of the effect of metiamide on pentagastrin stimulated and basal gastric secretion of acid and pepsin in man.
Gut 16:501-508

267. Thompson, M.H., Albinus, M., Blair, E.L., Reed, J.D. and Venables, C.W. (1975)
The interaction of cholinergic and histaminic blockade on the parietal cell:therapeutic possibilities.
Br.J.Surg.62:158

268. Tomassetti, P., Pazzaglia, M., Stanghillini, G., Bonara, G., Favaro, A., Vezzadini, P. and Labo, G. (1982)
Influence of ranitidine on serum gastrin and secretin levels in patients with duodenal ulcer.
World Congress of Gastroenterology, Stockholm, Abstract No.433:p109

269. Umezawa, H., Aoyagi, T., Morishima, H., Matsuzaki, M., Hamanda, M. and Takeuchi, T. (1970)
Pepstatin, a new pepsin inhibitor produced by actinomycetes.
J.Antibiotics 23:259-262

270. Uvnas, B. (1942)
The part played by the pyloric region in the cephalic phase of gastric secretion.
Acta. Physiol.Scand. 4 (Suppl.13):1-86

271. Valleur, P., Adam, M., Alasseur, M., Bitour, A., Hautefeuille, P. (1979)
Preliminary results in a series of thirty-three proximal vagotomies for duodenal ulcers not responding to cimetidine treatment.
Chirigie 105:685-688.

272. VanGordsenhaver, G., Wilkoff, L. and Kirsner, J.B. (1958)
Serum and urinary pepsinogen and gastric pepsin.
Gastroenterology 34:421-425

273. Vanrenterghem, Y., Roels, L. and Michielsen, P. (1980)
Prophylactic treatment with cimetidine after renal transplantation.
In: H_2-receptor Antagonists in Peptic Ulcer Disease and Progress in Histamine Research. (eds. Torsoli, A., Lucchelli, P.E., and Brimblecombe, R.W.). Excerpta Medica Amsterdam:pp159-163

274. Vanzant, F.R., Osterberg, A.E., Alverez, W.C. and Rivers, A.B. (1933)
Studies of gastric pepsin II secretion of pepsin in cases of duodenal ulcer and pseudoulcer.
J. Clin.Invest. 12:557-565

275. Vatier, J., Poitevin, C., Roberts, J.C. and Bonfils, S. (1982)
Role of antral histamine in the regulation of gastric effects of gastrin.
Gastroenterology 82:1204

276. Venables, C.W. (1969)
The relationship of pentagastrin stimulated pepsin secretion to duodenal ulceration.
Gut 10:1053

277. Venables, C.W., and Johnston, I.D.A. (1969)
The use of a combined pentagastrin insulin test to assess the effectiveness of truncal vagotomy.
Br.J.Surg. 56:701

278. Venables, C.W. (1971)
The secretion of pepsin I in peptic ulceration and its relationship to activity.
Br.J.Surg. 58:864

279. Venables, C.W. (1972)
An assessment of the value of measuring uncontrolled gastric secretion during routine secretion studies in man.
Br.J.Surg. 59:473-477

...142

280. Venables, C.W., Wheldon, E.J. and Johnston, I.D.A. (1975)
The pentagastrin insulin secretion test:its value in diagnosis and surgical management of recurrent ulceration following previous vagotomy.
Gut 16:830

281. Venables, C.W., Stephen, J.G., Blair, E.L., Reed, J.D., and Saunders, J.D. (1978)
Cimetidine in the treatment of duodenal ulceration and the relationship of this therapy to surgical management.
In: Cimetidine The Westminster Hospital Symposium. (eds.Wastell,C. and Lance, P.) Churchill Livingstone, Edinburgh:pp13-30

282. Venables, C.W. (1980)
Indications for surgery in duodenal ulcer nonresponders to cimetidine.
In: H_2-receptor Antagonists in Peptic Ulcer Disease and Progress in Histamine Research. (eds. Torsoli, A., Luccheli, P.E. and Brimblecombe, R.W.). Excerpta Medica Amsterdam:pp16-24

283. Venables, C.W. (1981)
Long-term management of duodenal ulcer - a surgeon's view.
In: Cimetidine in the 80's. (ed. Baron, J.H.) Churchill Livingstone, Edinburgh:pp113-122

284. Visik, A.H. (1948)
A study of the failures after gastrectomy.
Ann.Roy.Col.Surg.Eng. 3:266-284

285. Voegtlin, W.L. (1947)
Gastric acidity in normal individuals and those with uncomplicated duodenal ulcer:an attempt to influence the nocturnal secretion.
Gastroenterology 9:125-140

...143

286. Wald, A. and Burbige, E.J. (1974)
Benign gastric ulcers occurring with persistent histamine-fast achlorhydria.
Hopkins Med.J. 135:436-441

287. Walt, R.P., Male, P.J., Rawlings, J. Hunt, R.H., Milton-Thompson,G.J. and Misiewicz, J.J. (1981)
Comparison of the effects of ranitidine, cimetidine and placebo on the 24 hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer.
Gut 22:49-54

288. Walt, R.P., Trotman, I.F., Frost, R., Golding, P.L., Shepherd, T.H., Rawlings, J., Hunt, R.H., Colin-Jones, D.G., Milton-Thompson, G.J. and Misiewicz, J.J. (1981)
Comparison of twice daily ranitidine with standard cimetidine treatment of duodenal ulcer.
Gut 22:319-322

289. Watkinson, G. (1951)
A study of the changes in pH of gastric contents in peptic ulcer using the twenty-four hour test meal.
Gastroenterology 18:377-390

290. Watkinson, G. and James, A.H. (1951)
Twenty-four hour gastric analysis in patients with histamine achlorhydria.
Clin.Sc. 10:255-266

291. Webster, J., Petrie, J.C., Griffiths, R. (1980)
A combined clinical and pharmacokinetic study of cimetidine in patients with duodenal ulceration.
Scottish Medical Journal 25:81

....144

292. Winkelstein, A. (1935)
One hundred and sixty-nine studies in gastric secretion during the night.
Am.J.Dig.Dis. 1:778-782

293. Wilson, R.Y., Dymock, I.W. and Cowley, D.J. (1974)
Acid and pepsin dose response studies to insulin hypoglycaemia in a healthy man.
Digestion 11:90-97

294. Windus, A., and Vogt, W. (1907)
Sythese des Imidazolyl-äthyylamines.
Ber.dt.chem.Ges. 40:3691-3695

295. Wodehouse, P.G. (1921)
Jill the Reckless.
Herbert Jenkins Limited, London:126

296. Wolfer, A. (1881)
Gastroenterostomie
Zbl Chiv. 8:705-708

297. Woodward, E.R., Schapiro, H., and Armstrong, G. (1956)
Relation between uropepsin excretion and secretion in gastric juice.
J.Appl.Physiol.8:843-846

298. Wormsley, K.G., Mahoney, W.P., Ng, M. (1966)
Effects of a gastrin like peptide (ICI50123) on stomach and pancreas.
Lancet :993-996

299. Wormsley, K.G., Bovd. E.D.S., Peden, N.R. and Wilson, J.A. (1981)
Low dose ranitidine in the prevention of recurrence of duodenal ulcer.
In: The Clinical Use of Ranitidine. International Symposium, London.

....145

300. Wyllie, J.H., Clark, C.G., Alexander-Williams, J., Bell, P.F. Kennedy, T.L., Kirk, R.M., and Mackay, C. (1981)
Effect of cimetidine on surgery for duodenal ulcer.
Lancet 1:1307-1308

301. Yabaña, T. Kawaik (1982)
Effect of ranitidine on gastric acid and pepsin secretion stimulated by tetragastrin in duodenal ulcer patients and study group of gastric inhibition.
World Congress of Gastroenterology, Stockholm, Abstract No. 413:104

302. Yamagata, S., Ishimori, A., Sato, H., Okabe, H., Ishihara, K., Yugawa, N., Masuda, M., Kishikawa, M., Sakita, T., Ashizawa, S., Tsuneoka, K., Kaito, I., Wada, T., Namiki, M. (1973)
Clinical Evaluation of pharmacotherapy for peptic ulcer with antipepsin agents by double blind technique - multicentre clinical study.
Tohoku.J.Exp.Med. 110:377-404

303. Zollinger, R.M. and Ellison, E.H. (1955)
Primary peptic ulceration of the jejunum associated with islet cell tumours of the pancreas.
Ann.Surg. 142:709-728